From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
Subject: Re: AE for SUPPORT
Date: Wednesday, December 31, 2008 2:51:16 PM

Rose and Kris,
The SUPPORT AE I told you about (NN #[redacted] was not related to the study and was due to NEC.
Have a Happy New Year!!
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206[redacted]

From: Zaterka-Baxter, Kristin
To: Nancy Miller; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Alicia Guzman; Janet Morgan; Melissa Leps; Pablo Sanchez
Subject: RE: SUPPORT death
Date: Monday, December 29, 2008 10:47:52 AM

Thanks Nancy,
Do you know yet if it was considered at least possibly related to study?
Kris

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Monday, December 29, 2008 10:46 AM
To: Rose; Zaterka-Baxter, Kristin
Cc: Alicia Guzman; Janet Morgan; Melissa Leps; Pablo Sanchez
Subject: Re: SUPPORT death

Rose and Kris,
We had a death in the SUPPORT Study on (b) (6) . NN #(b) (6) . Since I was (b) (6) I don't know the circumstances. As soon as I get more information I'll get back with you.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
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UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT death
Date: Monday, December 22, 2008 1:45:28 PM

In follow up below – thanks,
Kris

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Monday, December 22, 2008 1:31 PM
To: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT death

Sorry, that is correct. This infant's death is not related to the study.

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, December 22, 2008 12:10 PM
To: Mcdavid, Georgia E; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kennedy, Kathleen A
Subject: RE: SUPPORT death

Thanks Georgia,
Just for confirmation and documentation, this death was not due to study correct?
Thanks,
Kris

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Monday, December 22, 2008 12:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Kennedy, Kathleen A
Subject: SUPPORT death

Patient (b) (6) was randomized in to the SUPPORT study on (b) (6) The infant was randomized in to the CPAP arm, however required intubation due to a precipitous delivery and low apgars. The infant died in less than 12 hours. Cause of death per medical team was extreme prematurity and pulmonary insufficiency. Medwatch to follow.

Georgia McDavid, R.N.
Senior Research Nurse-pediatrics/neonatology
Nurse Coordinator - NICHD Neonatal Network
MSB 3.252
office: 713-500-5734
office fax: 713-500-5794

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: isn"t there a SUPPORT trial conference call?
Date: Monday, December 22, 2008 1:06:33 PM

Hi Rose

Gerry Taylor and I are on the 675-(b) (6) line waiting for the SUPPORT conference call...is there a glitch?

Thanks

Susan

my cell is 650-799-(b) (6)

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Evans, Patricia W; Tyson, Jon E
Subject: RE: support
Date: Monday, December 22, 2008 11:01:49 AM

Rose,

(b) (6) was completed by Dallas on 12/11.
(b) (6) has had the neuro exam, and we are trying to get him back in for his Bayley to have a complete visit.
(b) (6) is currently MIA, but we're doing all we can to get him back in.

Thank you! Hope you have a great Christmas.

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713-500-6813 (office)
713-500-5794 (fax)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 19, 2008 2:45 PM
To: Kennedy, Kathleen A; Mcdavid, Georgia E; Tyson, Jon E; Evans, Patricia W; Poundstone, Margaret
Cc: Das, Abhik; Gantz, Marie
Subject: support

Hi,
We are missing a few SUPPORT outcomes. The trial is coming to an end and we would like to have missing data entered as quickly as possible. Please let us know how you are doing. Thanks for all the hard work and effort!!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18	[redacted]	FU window has closed but NF09a has not been completed
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: AP-ROP
Date: Monday, December 22, 2008 9:39:23 AM

Can you talley these?

From: nancy newman [mailto:nxs5@case.edu]
Sent: Monday, December 22, 2008 9:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: AP-ROP

This sounds like it would be better answered with SUPPORT data as we have detailed O2 and resuscitation info.....Nancy

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, December 22, 2008 9:25 AM
To: Barbara Stoll; Bell, Edward; Shankaran, Seetha; Laptook, Abbot; mcw3@cwru.edu; nancy newman; ellen_hale@oz.ped.emory.edu; adas@rti.org
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: FW: AP-ROP

Hi –
See the question below –
Let me know if GDB would wish to pursue or if this should be offered via SUPPORT as we have very accurate supplemental oxygen data. The aggressive posterior ROP may be reflective of more survival at lower gestational ages – SUPPORT cuts off at 24 weeks.

Thanks
Rose

From: Brian Darlow [mailto:brian.darlow@otago.ac.nz]
Sent: Saturday, December 20, 2008 2:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: AP-ROP

Dear Rosemary, It was good to meet in Washington.

What I was interested in was whether your Network may have a record of cases of AP-ROP over the last few years. It seems that this aggressive posterior form of ROP (Arch Ophthalmol 2005;123:991-9)might have become more common in recent years in the most immature babies. In former years it might have been called Rush disease or simply Zone I disease.

I wondered if it might be possible to carry out a case control study to look at resuscitation and exposure to 100% or similar high FiO2 from birth and for the first few hours of life, comparing AP-ROP cases with infants of the same gestation but no AP-ROP. Until recently all infants, including the most immature, were routinely resuscitated in 100% O2 and often babies would stay in high FiO2 for transport to the NICU. My hypothesis is that such exposure could cause extreme vasospasm in the retinal arteries of the most immature infants

and be a precursor to AP-ROP. We hardly ever saw this version of ROP until recently but it has apparently become more common in the last few years as more extremely preterm infants have been resuscitated and are surviving. Now that resuscitation practices have changed and many of us start in air and are guided by Sats it is possible fewer cases of AP-ROP will be seen. Unfortunately, there are too few cases of AP-ROP in the ANZNN Network to look at the issue and I wondered if there might be sufficient in your Network.

I would be interested in your thoughts.
Kindest regards, Brian Darlow

(I apologise for sending this to you rather late and after your meeting - I have been on service since my return)

Brian Darlow MD FRCP FRACP FRCPCH
Professor of Paediatrics
Christchurch School of Medicine
University of Otago Christchurch
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Christchurch 8140
New Zealand

Phone: (64 3) 3640 747
Fax: (64 3) 3644 907
E-mail: brian.darlow@otago.ac.nz
[Please note new e-mail address]

From: Vohr, Betty
To: Higgins, Rosemary (NIH/NICHD) [E]; Laptook, Abbot; Hensman, Angelita
Cc: Das, Abhik; Gantz, Marie; Aliksninis, Barbara
Subject: RE: SUPPORT
Date: Friday, December 19, 2008 4:11:33 PM

Thanks Rose. We have a great Team !
BV

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, December 19, 2008 3:41 PM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. The trial is coming to an end and we would like to have missing data entered as quickly as possible. Please let us know how you are doing. Thanks for all the hard work and effort!!
Given your outstanding recruitment, this is AMAZING!!!!!
Rose

CENTER	NETWORK	ROP_message
14	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
14	[redacted]	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Sood, Beena
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha
Cc: Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT
Date: Friday, December 19, 2008 3:37:12 PM

Dr Higgins – will look into this with Mary Johnson and get back to you.

Thanks
Beena

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 19, 2008 3:34 PM
To: Shankaran, Seetha; Sood, Beena
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

Hi,
We are missing a few SUPPORT outcomes. The trial is coming to an end and we would like to have missing data entered as quickly as possible. Please let us know how you are doing. Thanks for all the hard work and effort!!
Rose

CENTER	NETWORK	ROP_message
5	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
5	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

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

Blansfield, Earl (NIH/NICHD) [E]

From: Gantz, Marie <mgantz@rti.org>
Sent: Friday, December 19, 2008 3:19 PM
To: Finer, Neil
Cc: Das, Abhik
Subject: SUPPORT Updates
Attachments: SUPPORT Enrollment 12-16-08.doc; SUPPORT Adverse Events 12-16-08.doc; SUPPORT Protocol Deviations - old vs new 12-16-08.doc; SUPPORT Protocol Deviations by center - old vs new 12-16-08.doc; SUPPORT Use of HFNC 12-16-08.doc; All Centers pct in range through Dec08.rtf

Neil,

Attached are updates for SUPPORT for the Steering Committee meeting.

Happy holidays!

Marie

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

SUPPORT Enrollment as of December 16, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	1247	95%

Enrollment by Center

Center	<Jul-08	Jul-08	Aug-08	Sep-08	Oct-08	Nov-08	Dec-08	Total
3	95	2	2	1	1	0	3	104
4	61	2	2	1	0	0	1	67
5	56	1	4	3	2	1	0	67
8	17	0	0	0	0	0	0	17
9	72	1	5	1	1	4	2	86
11	82	1	1	1	3	2	0	90
12	60	2	2	0	3	0	0	67
13	28	3	1	1	0	1	1	35
14	110	0	0	2	1	7	0	120
15	41	3	2	0	4	2	2	54
16	159	7	2	1	4	2	0	175
18	73	1	1	1	1	2	1	80
19	53	2	1	1	0	1	0	58
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	61	1	3	0	0	1	3	69
23	45	0	0	1	1	2	0	49
24	24	1	0	0	0	0	1	26
25	45	0	1	3	0	0	0	49
26	14	1	0	0	0	2	0	17
Total	1113	28	27	17	21	27	14	1247
Centers		17	17	17	17	17	17	
Avg/center		1.6	1.6	1.0	1.2	1.6	0.8	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	1.9
2.5	1.5
3	1.2

Percent of SUPPORT infants with selected adverse events as of December 16, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.9	10.1	4.4
Air leak (pneumothorax, PIE, pneumopericardium)	9.7	12.6	7.6
Pulmonary hemorrhage	6.7	10.5	4.0
Severe IVH (grades III-IV)	14.4	20.5	10.0

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak (pneumothorax)	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	4
Surfactant not given in the first hour (surfactant group)	30
Surfactant not given in the first hour (CPAP group)	36
Oximeter not started within 2 hours	25
Infant received incorrect treatment assignment	16
Failure to use study oximeter at times required by protocol	84
Non-study (unmasked) oximeter used at same time as study oximeter	11
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate CPAP infant if all criteria met	4
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	26
Randomization/consent errors	26
Other	9
Total	293

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	95
Infant received incorrect treatment assignment	16
Failure to use study oximeter at times required by protocol	84
Non-study (unmasked) oximeter used at same time as study oximeter	11
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate infant if all criteria met	5
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	26
Randomization/consent errors	26
Other	9
Total	293

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	0
Surfactant not given in the first hour (surfactant group)	7
Surfactant not given in the first hour (CPAP group)	7
Oximeter not started within 2 hours	7
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	21
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2								1	1									4
Surfactant not given in the first hour (surfactant group)	2	4	2			3	1	3	2	1	3		1					5	3		30
Surfactant not given in the first hour (CPAP group)	4	2	1			3		1	7	3	4	1	1				1	5	2	1	36
Oximeter not started within 2 hours	1	1	2		1	1	2	1		2	2	2	2			1	2	1	4		25
Infant received incorrect treatment assignment	3		1			1	1			2	5		1				1		1		16
Failure to use study oximeter at times required by protocol	3	5	18		2	6	5	1	11	2	7		3				3	6	8	4	84
Non-study (unmasked) oximeter used at same time as study ox						2	1			1		1	3						3		11
Mechanical ventilation initiated for other than study criteria																	1		1		2
NSIMV initiated in infant not previously intubated	1				1			1			5										8
Extubation (excluding unplanned) for other than study criteria						2			5		2										9
Failure to extubate CPAP infant if all criteria met								1		3											4
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1		1								2
Infant received postnatal steroids in first 21 days of life	1					2		3	5		3	10	1				1				26
Randomization/consent errors		1	4		3	1				4		5	2			1	1				26
Other									3	1	2								2	1	9
Total	16	13	31	0	7	22	10	11	33	19	35	20	14	0	0	2	13	17	24	6	293

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – December 16, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			3%								1%	2%									0%
Surfactant not given in the first hour (surfactant group)	3%	7%	3%			4%	2%	9%	2%	2%	2%		2%					19%	6%		3%
Surfactant not given in the first hour (CPAP group)	5%	4%	1%			4%		3%	7%	6%	3%	2%	2%				2%	19%	4%	6%	4%
Oximeter not started within 2 hours	1%	2%	3%		1%	1%	4%	3%		4%	1%	3%	5%			4%	4%	4%	8%		3%
Infant received incorrect treatment assignment	4%		1%			1%	2%			4%	4%		2%				2%		2%		2%
Failure to use study oximeter at times required by protocol	4%	9%	27%		3%	8%	9%	3%	11%	4%	5%		7%				6%	23%	16%	24%	8%
Non-study (unmasked) oximeter used at same time as study ox						3%	2%			2%		2%	7%						6%		1%
Mechanical ventilation initiated for other than study criteria																	2%		2%		0%
NSIMV initiated in infant not previously intubated	1%				1%			3%			4%										1%
Extubation (excluding unplanned) for other than study criteria						3%			5%		1%										1%
Failure to extubate CPAP infant if all criteria met								3%		6%											0%
Failure to extubate surfactant infant if all criteria met						1%															0%
Infant intubated without meeting study criteria			1%								1%										0%
Infant received postnatal steroids in first 21 days of life	1%					3%		9%	5%		2%	16%	2%				2%				3%
Randomization/consent errors	1%	2%	6%		4%	1%				8%		8%	5%			4%	8%				3%
Other									3%	2%	1%								4%	6%	1%
Total protocol deviations	20%	23%	46%		10%	31%	18%	32%	34%	37%	26%	33%	33%		0%	7%	27%	65%	49%	85%	29%
Total number of infants enrolled	80	57	67	0	73	71	57	34	98	52	137	61	43	0	1	28	49	26	49	17	1000

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0
Surfactant not given in the first hour (surfactant group)	2			1		2	1				1										7
Surfactant not given in the first hour (CPAP group)	4			2												1					7
Oximeter not started within 2 hours						1					5	1									7
Infant received incorrect treatment assignment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1																			1
Other						1					1										2
Total	9	4	0	4	0	7	1	0	4	0	16	2	1	3	3	8	0	0	0	0	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0%
Surfactant not given in the first hour (surfactant group)	8%			6%		11%	10%				3%										3%
Surfactant not given in the first hour (CPAP group)	17%			12%												2%					3%
Oximeter not started within 2 hours						5%					13%	5%									3%
Infant received incorrect treatment assignment	4%			6%							11%					2%					3%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						6%
Non-study (unmasked) oximeter used at same time as study ox															14%						0%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							4%
Other						5%					3%										1%
Total protocol deviations	38%	40%		24%	0%	37%	10%	0%	18%	0%	42%	11%	7%	33%	43%	20%					25%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of December 16, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			4	5%
4			13	23%
5			10	15%
9			13	18%
11	1	5%	6	8%
12			9	16%
13			5	15%
14	1	5%	6	6%
15			1	2%
16			3	2%
18	1	5%	8	13%
19			9	21%
22			1	4%
23			1	2%
24			1	4%
25			8	16%
Total	3	1%	98	10%

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Oct08-Dec08	Days of life 1-14	All centers	4261	38.7	7.6	76.3	16.1
		Center 5	802	30.4	4.2	65.4	30.4
		Center 14	712	55.2	5.4	84.9	9.7
		Center 15	579	41.8	9.9	80.7	9.4
	Day 15 to 36 wks	All centers	17707	23.8	13.6	66.5	19.9
		Center 5	4018	28.0	9.2	63.5	27.3
		Center 15	2750	30.9	18.0	70.6	11.3
Jul08-Sep08	Days of life 1-14	All centers	10895	34.6	9.4	78.9	11.7
		Center 3	987	35.2	6.3	77.3	16.4
		Center 4	782	25.7	11.2	74.5	14.2
		Center 5	1060	20.7	8.8	71.1	20.2
		Center 9 site A	1234	37.9	10.8	79.5	9.8
		Center 13	1223	29.7	8.2	82.6	9.2
		Center 16	1778	48.4	9.3	84.7	6.0
	Day 15 to 36 wks	All centers	51905	25.8	13.2	67.2	19.6
		Center 3	4720	26.2	10.1	63.7	26.3
		Center 4	3211	30.4	13.0	70.8	16.1
		Center 5	5497	20.9	11.7	63.3	25.0
		Center 9 site A	3482	27.0	13.4	62.6	24.0
		Center 11	1460	14.8	14.3	54.9	30.8
		Center 12	2597	21.5	9.3	64.4	26.3
		Center 13	3063	20.6	12.4	72.5	15.1
		Center 14	1526	20.3	9.6	63.6	26.8
		Center 15	1783	28.7	15.7	64.5	19.8
		Center 16	7704	31.9	17.5	72.9	9.6
		Center 18	4819	28.5	16.3	67.6	16.1
		Center 25	3231	32.4	11.4	75.6	13.0
Apr08-Jun08	Days of life 1-14	All centers	13939	35.9	9.1	77.3	13.5
		Center 3	951	28.9	9.0	75.0	16.0

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 4	1139	53.0	2.9	81.5	15.7
		Center 5	1662	28.1	11.4	67.2	21.4
		Center 9 site A	718	48.8	9.4	83.1	7.5
		Center 11	881	16.9	8.8	65.7	25.6
		Center 14	863	37.6	7.3	82.9	9.9
		Center 16	1786	40.3	9.0	81.6	9.3
		Center 18	1052	26.2	7.2	74.4	18.5
		Center 25	1249	54.1	5.6	86.1	8.3
	Day 15 to 36 wks	All centers	60264	30.0	12.7	68.5	18.8
		Center 3	2628	31.1	16.3	67.6	16.2
		Center 4	3717	34.0	9.3	72.1	18.6
		Center 5	4458	24.9	9.9	64.5	25.6
		Center 9 site A	5473	33.5	13.5	71.2	15.3
		Center 11	2968	17.3	9.0	56.7	34.3
		Center 14	6557	36.0	9.0	70.9	20.1
		Center 15	3818	29.5	17.5	72.5	10.0
		Center 16	7841	33.6	12.0	75.5	12.5
		Center 18	1977	25.4	14.4	64.1	21.5
		Center 24	3433	19.5	22.4	56.7	20.9
		Center 25	9069	35.8	10.3	69.0	20.7
Jan08-Mar08	Days of life 1-14	All centers	9388	35.6	9.3	78.7	12.0
		Center 3	1241	38.6	8.9	78.3	12.9
		Center 5	829	23.5	7.7	66.4	25.9
		Center 11	901	24.7	10.2	76.9	13.0
		Center 14	591	51.6	4.7	83.5	11.7
		Center 16	1499	37.7	10.9	83.0	6.1
		Center 25	1064	51.7	4.2	85.4	10.3
	Day 15 to 36 wks	All centers	35919	27.8	14.2	67.2	18.6
		Center 3	4965	26.5	19.8	67.9	12.3
		Center 5	3691	28.3	11.8	66.1	22.1
		Center 11	2549	16.4	8.3	60.6	31.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 12	3255	37.2	11.0	68.5	20.5
		Center 14	1807	29.9	11.5	69.3	19.3
		Center 16	6947	29.0	15.7	72.4	11.8
		Center 18	4199	29.6	17.6	68.7	13.7
		Center 19	726	20.2	3.1	39.8	57.2
		Center 24	2859	23.7	15.1	63.9	21.0
		Center 25	924	26.1	8.8	79.3	11.9
Oct07-Dec07	Days of life 1-14	All centers	9501	31.5	9.2	76.9	13.9
		Center 3	1307	35.6	8.5	77.5	14.0
		Center 5	1741	32.6	7.7	70.9	21.4
		Center 16	2182	42.1	9.8	84.1	6.0
	Day 15 to 36 wks	All centers	44897	25.6	12.9	65.8	21.3
		Center 3	4597	33.0	14.2	69.4	16.4
		Center 5	8024	23.3	10.4	61.3	28.3
		Center 11	1138	24.6	10.2	54.4	35.4
		Center 12	1573	28.6	7.1	63.9	29.0
		Center 14	1386	20.9	13.3	63.9	22.8
		Center 15	2869	23.6	17.7	64.7	17.5
		Center 16	7237	26.1	14.6	70.7	14.7
		Center 18	1585	26.0	15.7	72.9	11.5
		Center 23	2680	28.8	10.8	61.4	27.8
		Center 25	6171	24.5	9.6	73.3	17.1
Jul07-Sep07	Days of life 1-14	All centers	15295	34.2	7.4	76.3	16.3
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1404	34.6	9.6	74.6	15.8
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9
		Center 16	1173	39.5	7.4	81.3	11.3
		Center 23	2150	32.6	5.5	71.6	23.0

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 25	2158	40.4	5.5	83.9	10.6
	Day 15 to 36 wks	All centers	56270	25.6	11.3	65.9	22.8
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5761	21.0	9.5	59.7	30.8
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	15479	34.1	9.0	76.5	14.5
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1062	31.1	11.5	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1439	40.3	8.5	85.7	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	1127	18.3	6.9	69.7	23.4
	Day 15 to 36 wks	All centers	56188	28.5	12.2	66.0	21.9
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		Center 11	4086	23.7	10.1	57.7	32.2

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Month	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	4710	29.9	13.1	69.8	17.1
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2857	22.4	9.4	55.4	35.2
Jan07-Mar07	Days of life 1-14	All centers	16863	35.4	8.3	78.0	13.6
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	54920	27.9	12.5	68.9	18.6
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8
		Center 16	3347	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	4307	20.2	17.7	64.5	17.8
Mar06-Dec06	Days of life 1-14	All centers	33182	37.3	8.1	79.1	12.8
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2456	33.1	9.1	67.8	23.1
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5671	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	881	30.5	6.0	77.5	16.6
		Center 25	1477	49.5	5.8	84.3	9.9
	Day 15 to 36 wks	All centers	107540	29.2	12.5	68.3	19.1
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3278	29.7	11.8	72.9	15.3
		Center 11	6552	28.9	10.3	61.6	28.1
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14378	29.3	12.5	69.1	18.4
		Center 18	14879	24.1	17.0	66.3	16.8
		Center 19	1695	24.5	7.9	56.8	35.3
		Center 25	6484	39.9	9.3	77.0	13.7
Through Feb06	Days of life 1-14	All centers	27099	38.1	9.3	79.6	11.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/18/08)

Month	Time on supplemental oxygen	Center Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-86	Percent >86
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1448	32.0	10.0	77.5	12.5
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1517	42.1	9.5	85.5	5.0
		Center 22	3586	40.3	8.6	80.1	11.3
	Day 15 to 36 wks	All centers	133420	26.5	12.2	67.6	20.2
		Center 3	13570	17.7	17.4	64.2	18.4
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	5473	19.1	9.2	58.6	32.1
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	8688	28.1	17.8	63.6	18.6
		Center 19	1280	35.4	7.7	77.5	14.9
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	3563	29.6	16.7	68.7	14.6
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Addition to SAE for SUPPORT
Date: Friday, December 19, 2008 1:32:24 PM

Yes.

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Is this the infant with the infarction?

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Friday, December 19, 2008 1:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Subject: Addition to SAE for SUPPORT

Dear Rose,
We have just located additional information for the SAE for SUPPORT subject (b) (6) There was an earlier head u/s done on (b) (6) that was not entered into computer till today. The report of this first u/s is normal head ultrasound.
Ellen

Ellen Hale, RN, BS, CCRC

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

Ellen Hale, RN, BS, CCRC

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg
Subject: support secondary
Date: Thursday, December 18, 2008 3:54:43 PM
Attachments: rop concept12-18-08.doc

(See attached file: rop concept12-18-08.doc)

here's the concept summary for sample collection with support for rop gwas

mc

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Do Genetic Variations Influence ROP risk at High vs. Low Oxygen Saturation Target Range?

CM Cotten, J Dagle (co - PI's)
T Young, S Mohammed, T Yankovitch, K Schibler, RN Goldberg, G Ginsburg, M Hauser, E Bell, J Murray

Synopsis

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness among extremely low gestational age (< 28 weeks gestation) infants in countries with established market economies (e.g., UK, USA, Canada), and is a rapidly increasing problem in countries where survival among infants born at 28 – 32 weeks gestational age is increasing. Epidemiologic studies reinforce *in vivo* animal experiments that demonstrate postnatal oxygen exposure contributes to risk of ROP in both gestational age groups. Epidemiologic studies in mono- and di-zygotic prematurely born twins indicate that two-thirds or more of an individual preterm infant's risk of ROP can be attributed to genetic variation, and candidate gene studies have identified specific biologically plausible risk alleles. Gaining understanding of how genetic variation and oxygen exposure interact to influence risk of ROP could lead to improved screening, prevention, and treatment strategies for ROP in all gestational age groups. In the coming months, the NICHD Neonatal Research Network's SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) clinical trial will have completed enrollment of 1300 extremely low gestational age infants randomized to one of two target oxygen saturation arms, and collected an unprecedented amount of oxygen exposure and continuous oxygen saturation monitoring data on each infant. Extensive data on ROP phenotype, as well as long term (> 3 years) neurodevelopmental and neuroimaging follow-up is planned and will likely be available for at least 800 of the surviving infants. For this study, we propose that DNA samples be collected when infants return for follow-up visits. An unbiased genome wide scan will be made to identify loci associated with ROP. The analysis will assess interactions between the randomized oxygen intervention and identified loci and associations with ROP. This study has great potential to confirm suspected pathways and mechanisms of disease and identify novel mechanisms in the context of 2 different levels of oxygen exposure. Our hypothesis is that genetic variations will be associated with ROP risk, and their effects will vary in the two oxygen exposure groups.

Background & Significance – Evidence for oxygen exposure influencing risk of ROP among extremely premature infants is strong. Recent studies suggest lower oxygen saturation targets may be protective against development of ROP, and later lower oxygen targets may be protective against lung injury without significantly adding to risk of worse ROP outcome. (Phelps 2000, Askie 2003). Other studies indicate management with lower oxygen saturation targets throughout the NICU stay may reduce ROP risk without increasing risk of mortality or other morbidities, but even with reduction in oxygen exposure, disease is not eliminated completely. (Tin 2001, Chow 2003)

Holmström et al, have provided a summary of epidemiologic studies, candidate gene analyses, and genetic manipulations of animal models that provide a compelling argument for further investigation of genetic variations that contribute to ROP pathogenesis (Holmström 2007) Some of the reviewed studies are briefly described below.

In a multicenter study of prevalence of ROP among mono- compared with di-zygotic twins born prior to 32 weeks post conception. (Bizarro 2007) In the mixed-effects logistic regression analysis for ROP, gestational age and duration of supplemental oxygen use were significant covariates. After controlling for known and unknown nongenetic factors, genetic factors accounted for 70.1% of the variance in liability for ROP. In a recent family based study in Mohamed et al, using samples from 330 preterm infants from a single current Network center identified 6 single nucleotide polymorphisms (SNPs) in six candidate genes associated with development of ROP. Included in these was a protective polymorphism in the complement factor H (CFH) gene. (Mohamed 2008) Other CFH SNPs have been associated with risk of age related macular degeneration (AMD). (Spencer 2007)

Candidate gene analyses testing genetic variations in genes that investigators hypothesize have a major role in ROP development have also revealed promising results that need further clarification and validation in larger sample size populations. (Ioannides 2001) Cooke et al published a positive association between a VEGF polymorphism (VEGF-634 G/C) and risk of treatment for threshold ROP. (Cooke 2004) This study did not account for environmental covariates including oxygen use. Accounting for multiple factors will require large sample sizes as well as accurate exposure data as well as outcome. Investigators have also described a genetic polymorphism that is linked to low IGF-1 levels and IUGR, both of which have been linked with ROP. (Hellstrom 2001, 2003, 2004) The IGF-1 allele 191, a cytosine-thymine repeat in the intronic region of the gene between exons 2 and 3, was present in 8.5% of the sample of 124 Dutch children and their parents, and it was associated with reduction in birth weight, length, and head circumference. This association has not been assessed in growing premature infants. (Arends 2002) Variation from another site of variation, this one in the promoter region of the IGF-1 gene has been associated with lower birth weight in other populations, as well as age-related IGF-1 decline in adults. (Rietveld 2003) This polymorphism was not associated with growth restriction in the study by Arends et al (Arends 2002) and has not been assessed for association with ROP.

As a primary aim of the SUPPORT trial, ROP data is collected through 55 weeks postmenstrual age when eyes should be fully vascularized (SUPPORT Manual of Operations, Chapter 15). This outcome data, based on the ETROP study intervention criteria (Good 2003), will be among the most robust ROP phenotype data available in any study cohort with corresponding exhaustive detailed data on oxygen exposure with potential for DNA collection and analysis. For acceptable genomic association studies, a well defined phenotype is crucial to study plausibility. The opportunity to use an unbiased genome wide screening technique to identify potentially biologically plausible genetic variants that interact with oxygen exposure is unique and important. Using salivary collection techniques, adequate DNA samples can be obtained during follow-up visits for these infants.

Significance- ROP continues to be a leading cause of blindness among extremely preterm infants in the developed world, and is rapidly increasing among later gestation preterm infants in countries with emerging economies. (Gilbert 2008) Screening for the disease is labor intensive and the supply of appropriate screeners using current techniques and epidemiologic risk identification is dropping to critically low levels. (Kemper 2008) Identifying optimal prevention and treatment strategies will be important. By taking advantage of the opportunity afforded by the robust data collection on oxygen exposure and ROP phenotype in the SUPPORT trial, the proposed study will provide

insights into pathophysiology of ROP that will greatly enhance and economize our approach to screening, treating, and ultimately, preventing ROP.

Study design – The study will be a prospective cohort study to identify associations between genetic variants and retinopathy of prematurity.

Study population
Inclusion criteria
The inclusion criteria include infants who were enrolled in the SUPPORT trial, and are being seen in follow-up for neurodevelopmental and neuroimaging outcomes, and whose parent/guardian provides written informed consent.

Exclusion criteria
Infants not enrolled in the SUPPORT trial.

Methods.
When infants return for follow-up, they will be approached for consent to participate in the ROP-oxygen genomics study by study staff at participating sites. For those that provide written informed consent, samples will be collected with an Oragene swab using standardized protocols which provide a consistent yield of over 3 ug of genomic DNA which would be an optimal amount for genome wide assessment with > 1 ug genomic DNA remaining. (Oragene white paper: http://www.dnagenotek.com/pdf_files/PD-WP-007_DNA%20yield%20using%20sponges%20whitepaper_Issue%201_1.pdf) In addition, DNA samples will be collected from available parents. Samples will be labeled with a bar code label allocated from the Duke Center for Human Genetics (CHG) as part of the CHG Sample Acquisition Form (SAF), which is maintained always at the study site. The SAF will link the subject's identify to the bar code number and the subject's assigned Network number. The site will provide the linked Network number and the SAF number to the data coordinating center, so that when the sample is logged in at Duke CHG, information derived from the sample can be sent to RTI and linked with previously collected information about that subject.

Once at Duke CHG, DNA will be extracted from Oragene swabs using standardized methods and assessed for quality. The plan will be to conduct a genome wide scan on the purified DNA samples using the current Illumina Whole Genome Infinium® Assay which relies on the use of tagSNPs, (loci that can serve as proxies for many other SNPs). Genotypes will then be assessed for their independent associations with ROP, and then assessed in multivariable models including high and low oxygen range.

Because the study will use genome wide scans for the entire genome, there is a chance that the genotyping will uncover genetic variants linked to known disease risk in some study participants. In the consent form, subjects' parents/guardians will be informed that the genotyping is for research purposes only, but there is a small chance for incidental findings related to an inherited risk for a disease known at the time of testing to be likely to cause premature death if untreated. The possibility of incidental findings will be included in the consent process, and contact information for accessibility to genetic counseling at Network sites will be made available.

Sample size calculation
Planned enrollment for the SUPPORT trial is 1310. If 60% of an estimated 900 SUPPORT surviving infants who are seen in follow-up can be enrolled, approximately

720 of an estimated 900 survivors to discharge with final eye diagnosis will be available. Only one sibling of any sibship or multiple birth within the study population can be included in the genomic analysis of the cohort. The estimated percentage of multiple births in the SUPPORT trial based on prior Network demographic reports is 25% leaving an estimated 540 infants + single representatives of the sibships/multiple births (estimate of 60 added infants) = 600 for the final genomic analyses.

Of this 600, with an estimated prevalence of > Stage III ROP (the definition of the ROP portion of the primarly outcome for the SUPPORT trial) is 25% based on the results included in the 2007 GDB site reports for ELBW infants. If this estimate is accurate, we are likely to have 150 infants with > Stage III ROP. Our analysis plan is to test associations between alleles and the primary ROP outcome, in multivariable models, along with covariables including gestational age, race/ethnicity, gender, and High or Low Oxygen Group.

Additional information can be gleaned from the genotypes with assessment for other outcomes that were collected in SUPPORT, including bronchopulmonary dysplasia as well as neuroimaging and neurodevelopmental outcomes which have been demonstrated to have plausible genetic contributions to risk, either through twin studies (BPD; Bhandari 2007, Lavoie 2008) or candidate gene analyses (cerebral palsy; Gibson 2008). These analyses will be more exploratory than the ROP analysis, as there are major concerns that infants with the most significant pulmonary or neurologic injuries will not have survived to follow-up.

Budget – We base our budget calculations on the following sample numbers:
We expect to enroll and collect samples from 600 subjects and one parent from ½ of families, and two parents from the other ½. We estimate of 25% of subjects will be products of multiple births, so 600 infants from 525 families will be enrolled. Parent numbers are then estimated to be 263 single parent families, and 262 two parent families, for a total of 787 parent samples. The total samples to be included then is 787 parent samples + 600 infant samples = 1387 samples.

- 1400 CHG SAF forms @ $2 each = $2800
- Coordinator time for consent, collection, storage on site, batch mailings—2 hours per family x 525 families @ $35hr = $36,750.
- Oragene salivary samples, includes sign-in, EQ, Quantitation, and Storage of DNA, 1400 estimated samples @ $36.00 per sample = $50,400
- Batch mailing on dry ice: 2 mailings per center for dry ice and overnight FEdEX, @ $165/shipment x 32 mailings to CHG = $5280

Total to collect samples and extract DNA ready for genotyping: $95,320.

- Genotyping and Genome Wide Scan using 650 SNP Illumina platform: *TBD*

References.

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From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Subject: SAE for SUPPORT
Date: Thursday, December 18, 2008 2:00:32 PM
Attachments: scan.jpg
IRB SAE documentation 12.15.08.doc

Rose,
Please find attached summary and Medwatch for SUPPORT SAE that We talked about yesterday.
Ellen

Ellen Hale, RN, BS, CCRC

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

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

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899-9707 pager

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

MEDWATCH FORM

SUPP08A Rel 1.0
January 4, 2005

Center: 09 Site No: (b) (6) Network No: (b) (6) Birth No: 1 Mother's Initials: ___ ___ ___ Page 1 of 1

SEND TO RTI AND NICHD WITHIN 24 HOURS

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires: 11/30/99
See OMB statement on reverse

FDA Use Only
Triage unit sequence #

A. Patient information

1. Patient Identifier	2. Age at time of event: or Date of birth	3. Sex	4. Weight
(b) (6) In confidence	(b) (6)	☒ female ☐ male	___ lbs or 1.030 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death ___ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☒ other: unknown

3. Date of event (mo/day/yr): (b) (6)

4. Date of this report (mo/day/yr): (b) (6)

5. Describe event or problem

See attached Summary

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) (do/da (or best estimate))
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

N/A

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- ☐ health professional
- ☐ lay user/patient
- ☐ other:

5. Expiration date (mo/day/yr)

6. model # ___
catalog # ___
serial # ___
lot # ___
other # ___

N/A

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)
Masimo Study Pulse Oximeter

E. Reporter (see confidentiality section on back)

1. Name & address
Ellen Hale, RN
49 Jesse Hill Jr. Drive SE
Atlanta, GA 30303
phone # (404) 616-4218

2. Health professional? ☒ yes ☐ no

3. Occupation: Research RN

4. Also reported to
- ☐ manufacturer
- ☐ user facility
- ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. ☐

PLEASE TYPE OR USE BLACK INK

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

December 18, 2008

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

RE: Severe Adverse Event

Center 09 **Rand.** (b) (6) **Network** (b) (6)

On 11/21/2008 antenatal signed informed consent and HIPPA authorization were obtained from this mother for this study in anticipation of delivery prior to 28 weeks gestation. This mother was discharged on (b) (6) On the morning of (b) (6), mom went into preterm labor and arrived at the hospital fully dilated, infant was breech presentation, and emergency c/s was performed. This infant was randomized to the "Early Extubation and CPAP" arm of this NICHD study. This infant was a 1030 gram female infant of 26 4/7 weeks gestation. She had APGAR scores of 6 at one minute and 9 at five minutes. In the delivery room this little girl required positive pressure ventilation via neo-puff and was transitioned to CPAP and taken to the NICU. She was placed on a Masimo study pulse oximeter (serial #313092). About 4 hours later she met criteria for intubation and was intubated and given a dose of surfactant. She received a total of 3 doses of surfactant. On (b) (6) infant was placed on high frequency ventilation. This infant continued to require HFV and FiO2 ranging from 30-100%. On (b) (6) infant was started on INO. A head ultrasound on (b) (6) revealed "1.5 X 2 cm hypoechoic area within the left periventricular white matter posteriorly determined to be an infarction per attending." No IVH was noted. On (b) (6) infant continues to require HFV and high FiO2 (to 100%) and INO.

This case was reviewed with Dr. Susie Buchter and the event was not attributable to SUPPORT Study.

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing outcomes
Date: Thursday, December 18, 2008 1:27:14 PM
Attachments: Infants with missing outcomes 12-18-08.xls

Rose,

Attached is the list of SUPPORT infants with missing outcomes this month.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
4	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The patient is within their Fol-up window and final ROP status has not been reported.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		The patient is within their Fol-up window and final ROP status has not been reported.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient is within their Fol-up window and final ROP status has not been reported.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		The patient is within their Fol-up window and final ROP status has not been reported.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SAE
Date: Thursday, December 11, 2008 1:40:13 PM

Will do.
Ellen

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Yes
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Dec 11 13:34:37 2008
Subject: Re: SUPPORT SAE

Rose,
Our little baby is better and on CPAP today. We have reported the PIE on the SUPP08. Do we need to complete the medwatch and send a summary.
Thanks,
Ellen

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Great
Have Ellen send the AE when she returns

Rose
Rosemary D. Higgins, MD
Program Scientist

From: Michelle Tidwell
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Ellen Hale
Sent: Mon Dec 08 11:40:33 2008
Subject: Re: SUPPORT SAE

The baby is stable today. He had to be placed on high frequency over the weekend. He should be extubating later today. No pulmonary hemorrhage and no IVH on last head ultrasound. Baby previously had a pneumomediastinum and a pneumothorax which Ellen reported. Mom was

[illegible] ruptured about 2 wks PTD.

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899-9707 pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Is the infant stable at this time? Was there any IVH or pulmonary hemorrhage?

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Michelle Tidwell
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; Ellen Hale
Sent: Mon Dec 08 11:30:25 2008
Subject: SUPPORT SAE

Good Morning,

Ellen is out of the office today. I wanted to let you both know about a SUPPORT SAE. Baby #7896 was diagnosed with PIE on 12/5 and per study PI it is not attributable to the SUPPORT study. Please let me know if you need additional information before Ellen returns on Wednesday. Thanks!

Michelle

Michelle Tidwell, RN, BSN
Research Nurse
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(404) 616-5397 office (404) 899-9707 pager

Ellen Hale, RN, BS, CCRC

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Ellen Hale, RN, BS, CCRC

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: CTSA and support at your institution
Date: Sunday, December 07, 2008 7:41:55 PM

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/4/08 3:25 PM >>>
Hi,

We traditionally list grant numbers that give SUPPORT in our NRN papers.
In an effort to insure accuracy, please let me know the following:

1. Do you have a current CTSA at your site? (Or at affiliated sites)?

_x__ yes ___no

2. Does the NRN project at yet site receive CTSA support?

___yes _x__no

If yes, what type of support:
_____ research nurse/staff salary support

_____ lab support for studies

_____ funded other investigator (K12)

_____ other

Please feel free to add additional comments.

Try to respond by December 15.

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B; Dusick, Anna M.
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Wednesday, December 03, 2008 1:00:56 PM

This Follow-up visit was a home visit completed on Nov 10th. It has been keyed into the system. Thanks

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 26, 2008 10:16 AM
To: Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	FU_message
12	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Evans, Patricia W
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poundstone, Margaret
Subject: FW: SUPPORT
Date: Tuesday, December 02, 2008 12:19:48 PM

The following is an update on the missing Support babies. We'll continue to work on the last 3 until all efforts are exhausted.

All the best,

Patricia W. Evans, MD
Assistant Professor of Pediatrics, Division of Neonatology
The University of Texas Medical School at Houston
713-500-5311 (office)
713-500-5794 (fax)
Patricia.W.Evans@uth.tmc.edu (e-mail)

Eco-Tip (from IdealBite.com): Every year 1.5 million barrels of oil go into making plastic water bottles and less than a quarter of those are recycled. So kick the bottled water habit and choose a reusable bottle instead.

From: Poundstone, Margaret
Sent: Tuesday, December 02, 2008 11:17 AM
To: Evans, Patricia W
Subject: RE: SUPPORT

(b) (6) – Lost to f/u. I thought he had been declared, but he wasn't. I just did that.
(b) (6) – That's (b) (6) who will be seen by Dallas. Janet said she would do the questionnaire.
(b) (6) – This baby is one of our pending. We haven't talked to mom since August 22. She was scheduled to come in but no-showed. We haven't been able to get in touch with her, b/c she doesn't' have any valid numbers. We'll need to send a letter.
(b) (6) – this baby's parents live on a ranch somewhere (b) (6) (last time we heard). We have no valid #'s and the letter from the Medicaid address was returned.

Margaret Layne Poundstone, RN, BSN
University of Texas Medical School - Houston
Coordinator, Neonatal Research Follow-Up Program
6431 Fannin Street, Suite 3.252
Houston, Texas 77030
713-500-6813 (office)
713-500-5794 (fax)
Margaret.Poundstone@uth.tmc.edu (e-mail)

From: Evans, Patricia W
Sent: Wednesday, November 26, 2008 10:59 AM
To: Poundstone, Margaret ; Alaniz, Nora I
Subject: FW: SUPPORT

Any updates on these babies?

Patricia W. Evans, MD
Assistant Professor of Pediatrics, Division of Neonatology
The University of Texas Medical School at Houston
713-500-5311 (office)
713-500-5794 (fax)
Patricia.W.Evans@uth.tmc.edu (e-mail)

Eco-Tip (from IdealBite.com): Every year 1.5 million barrels of oil go into making plastic water bottles and less than a quarter of those are recycled. So kick the bottled water habit and choose a reusable bottle instead.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 26, 2008 9:22 AM
To: Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E; Tyson, Jon E
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
18		Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18		FU window has closed but NF05 and NF09a have not been completed
18		FU window has closed but NF09a has not been completed
18		FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Kimberley A Fisher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michael Cotten; Katherine A Foy; Ronald N Goldberg; golds005@mc.duke.edu; lohme001@mc.duke.edu; Gantz, Marie
Subject: Re: SUPPORT
Date: Friday, November 28, 2008 1:53:39 PM

Rose
Please see the response in red to the queries listed below.

One of my employees is currently entering data for GDB and will transmit the info today before she leave the office.

thanks
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC
Clinical Research Operations Director
Dept of Pediatrics/Neonatology
Clinical Associate Professor/SON
DUMC 3179
Durham, NC 27710
Work: 919-681-4913
Fax: 919-681-4868
Pager: 919-970-1743
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

11/26/2008 10:23 AM

To "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, <golds005@mc.duke.edu>, "Katherine A Foy" <foy00004@mc.duke.edu>, <lohme001@mc.duke.edu>, "Kimberley Fisher" <Kimberley.fisher@duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>
Subject SUPPORT

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER NETWORK ROP_message

19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status. This child came for follow up visit but had not been seen for FU for ROP - the database was corrected to show this

CENTER NETWORK BPD_message

19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing This info was corrected in database and is now complete

CENTER NETWORK FU_message

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed This info was corrected in the database and is now complete

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; Julie Rohr; Gantz, Marie
Cc: Conra Lacy; Kristi Watterberg; Das, Abhik; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Missing SUPPORT Primary Outcomes
Date: Wednesday, November 26, 2008 1:12:38 PM

I think Marie and I can discuss this and work in the withdrawal code into the programming. There shouldn't be anything else NM needs to do for this case.

Thanks, Jenny

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 26, 2008 12:56 PM
To: Julie Rohr; Auman, Jeanette O.; Gantz, Marie
Cc: Conra Lacy; Kristi Watterberg; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: Missing SUPPORT Primary Outcomes

Any other way to code this one?
Thanks
Rose

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Wednesday, November 26, 2008 12:32 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Conra Lacy; Kristi Watterberg
Subject: Missing SUPPORT Primary Outcomes

Hi Rose,
Regarding the missing ROP outcomes:
Patient (b) (6) is our patient that withdrew from the study due to the oximeter issues (and then transferred to Phoenix). Mom had said that we could use data collected up to the point that she withdrew from the study but then we could collect no more data.

On the outcome status form (SUPP 09) we coded the outcome on question A1 as "6-withdrawn from study". We are unaware of any other form or way to enter again that the patient withdrew from the study so that it is clear that ROP exam data won't be forthcoming.

If there is some other way we can communicate this please let us know. Also, please feel free to contact me if you need more information regarding this.

Have a great Thanksgiving!

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

From: Karen Osborne RN
To: Higgins, Rosemary (NIH/NICHD) [E]; Bradley Yoder; Roger Faix; abodnar@utah.gov
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Wednesday, November 26, 2008 1:07:40 PM

Hi,

(b) (6) Withdrew from the SUPPORT study (in the first week) so is not eligible for FU
Has been seen and the data was keyed on 11/20
Has moved to Florida. Visiting Utah in the spring so FU visit will done at that time
Has been seen and the data was keyed on 11/21
This patient is lost to follow up after divorce of parents and moved out of state.

Please let me know if you need more info.

Karen

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 26, 2008 8:28 AM
To: Bradley Yoder; Roger Faix; Karen Osborne RN; abodnar@utah.gov
Cc: Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	FU_message
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
25	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

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

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@case.edu; "nancy newman"
Subject: RE: SUPPORT OUTCOMES
Date: Wednesday, November 26, 2008 11:18:06 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 26, 2008 10:10 AM
To: mcw3@cwru.edu; nancy newman; Bonnie Siner
Cc: Gantz, Marie
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing. This is incredible given your outstanding recruitment!!!!
Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.-already entered
3	[redacted]	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.-waiting for report from ophthalmology
CENTER	NETWORK	BPD_message
3	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered) -not d/c'd home yet; data not completed

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higginsr@mail.nih.gov

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
Subject: Re: SUPPORT AE
Date: Wednesday, November 26, 2008 10:35:22 AM

Rose and Kris,
I'm sending a MedWatch for NN# (b) (6) It's for PIE and it's not related to the study. Unfortunately, I didn't catch this until I was completing the discharge information.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206-(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bell, Edward"; "Johnson, Karen"
Cc: "Gantz, Marie"
Subject: SUPPORT
Date: Wednesday, November 26, 2008 10:25:42 AM

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
24	(b) (6)	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
24	[redacted]	The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
24	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Ronald N Goldberg"; "Michael Cotten"; "gokds005@mc.duke.edu"; "Katherine A Foy"; "lohme001@mc.duke.edu"; "Kimberley Fisher"
Cc: "Gantz, Marie"
Subject: SUPPORT
Date: Wednesday, November 26, 2008 10:23:21 AM

Hi,
We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.
Thanks for all the effort!
Rose

CENTER	NETWORK	ROP_message
19	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
CENTER	NETWORK	BPD_message
19	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing
CENTER	NETWORK	FU_message
19	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

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

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kathleen A Kennedy"; "Evans, Patricia W"; "Georgia McDavid"; "Tyson, Jon E"
Cc: "Gantz, Marie"
Subject: SUPPORT
Date: Wednesday, November 26, 2008 10:21:46 AM

Hi,

We are missing a few SUPPORT PRIMARY OUTCOMES. Let us know how you are doing.

Thanks for all the effort!
Rose

CENTER

NETWORK

ROP_message

18

(b) (6)

The patient is within their Fol-up window and final ROP status has not been reported.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

18

(b) (6)

Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

18

(b) (6)

Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

CENTER

NETWORK

FU_message

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

18

(b) (6)

FU window has closed but NF09a has not been completed

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Finer, Neil
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Support randomization question
Date: Saturday, November 22, 2008 7:39:12 PM

It sounds as if Rose and the others feel that this child should be out – I understand that the infants need to be enrolled within 2 hours, but in view of the consent, would have been OK with including. I will go along with the others to avoid any confusion.
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Saturday, November 22, 2008 3:19 PM
To: Finer, Neil; higginsr@mail.nih.gov
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Support randomization question

Hi Neil,
I unfortunately already told UAB to take the baby off the study oximeter based on Ken's, Abhik's and Rose's discussion; should I ask UAB to place the baby back on the study oximeter? It's been about 48 hours since I asked they take the baby off.
Thanks.
Kris

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Saturday, November 22, 2008 1:52 PM
To: Zaterka-Baxter, Kristin; higginsr@mail.nih.gov
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Support randomization question

Hi Kris
I would probably prefer that the infant be left in the trial and protocol deviation noted. I assume that the infant did nor receive CPAP prior to 7:30 the following morning? Our analyses will also be by intent to treat. There is a concern that the infant did not receive early CPAP and this is a problem but I would note and continue.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 17, 2008 11:12 AM
To: higginsr@mail.nih.gov; Finer, Neil
Cc: Das, Abhik; Gantz, Marie
Subject: Support randomization question
Importance: High

HI,
UAB consented a mom a couple of weeks ago to Support; the mom delivered (b) (6) at 8:30PM but was not randomized by the respiratory team. This was discovered by the research team at (b) (6) (b) (6), a randomization card was pulled (CPAP arm) and a study oximeter was placed. The infant was place on CPAP at 0730; prior to the randomization the baby was on oxygen and not vented. In past cases we have asked that a protocol deviation be completed and the infant stayed on study but typically the randomization occurred within the 2 hour window for oximeter placement. Please advise whether this infant should remain on study or be counted as a missed case.
Thanks,
Kris

Kris Zaterka-Baxter
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P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT SAE
Date: Friday, November 21, 2008 4:30:15 PM

Only SAE received today was the hard copy to this report below –

Thanks,

Kris

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Tuesday, November 18, 2008 2:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Susie Buchter
Subject: SUPPORT SAE

Dear Rose,
One of our SUPPORT babies died this morning secondary to pulmonary hemorrhage. This was baby (b) (6) We have discussed this death with Susie and cause of death is not related to study. Infant was on day (b) (6) of study. We will be sending the medwatch and summary.
Ellen

Ellen Hale, RN, BS, CCRC

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Gantz, Marie
To: Wilson, Leslie Dawn
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.; Newman, Jamie
Subject: RE: SUPPORT
Date: Thursday, November 20, 2008 1:34:57 PM

Leslie,

I see that the infant in question died after discharge. There is an NF12 for the infant; however, there is not an NF10. Please complete an NF10 as well. Thanks!

Marie

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:35 PM
To: Wilson, Leslie Dawn; Poindexter, Brenda B
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT

So they did not consent for breathing outcomes, correct? If so, those forms should be deleted. Was the death an in-hospital or post-discharge death? If in-hospital, it should get reflected on GDB. If post-discharge, we will need the NF-12 3.b filled out.

Thanks
Rose

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Wednesday, October 22, 2008 4:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Das, Abhik; Marie Gantz
Subject: RE: SUPPORT

Hi. This infant passed away (b) (6) For Breathing Outcomes, there was a SUPP01, 02, and 03 completed, stating that the interviews were not done because of the death. I had requested that even this be removed from the network database as there was no consent obtained for pt to ever be in this sub-study.

Thank you-leslie

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:14 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing Outcomes
Date: Thursday, November 20, 2008 12:50:40 PM
Attachments: Infants with missing outcomes 11-20-08.xls

Rose,

Attached is the list of SUPPORT infants who have missing outcomes this month.

Thanks,
Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
3		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
4		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
22		The patient is within their Fol-up window and final ROP status has not been reported.
22		The patient is within their Fol-up window and final ROP status has not been reported.
24		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
24		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
26		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Laptook, Abbot
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hensman, Angelita
Subject: RE: support infant
Date: Wednesday, November 19, 2008 10:00:28 AM

---

got it, tx, AL

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, November 18, 2008 7:07 PM
To: Laptook, Abbot
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support infant

Hi Abbot
I would take the infant off the study oximeter and follow the cardiology advice. Sorry for the delay I just got back from Australia. In addition, this infant would not be informative regarding the oximetry arm because of his fixed shunt.
Neil

From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Tuesday, November 18, 2008 8:21 AM
To: Finer, Neil
Cc: HigginsR@mail.nih.gov; Hensman, Angelita
Subject: support infant

Neil
Need some guidance regarding an infant in the support trial, (b) (6) who was diagnosed with a (b) (6) some time after birth. The Cardiologists would like the range of oxygen saturations used to care for the infant from 80-88%. I don't see how we can keep the infant on the study pulse oximeter with this desired range of saturations. Does the infant come off the study pulse oximeter? Let me know, AL

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From: Zaterka-Baxter, Kristin
To: Shirley Cosby
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: RE: Support randomization question
Date: Tuesday, November 18, 2008 3:28:12 PM

Hi Shirley,
The consensus is that this baby should not be enrolled in the Support study primarily because they were well outside the 2 hour window for oximeter placement.

Thanks so much for all the effort - appreciate it!
Kris

From: Shirley Cosby [mailto:SCosby@peds.uab.edu]
Sent: Mon 11/17/2008 4:25 PM
To: Zaterka-Baxter, Kristin
Subject: RE: Support randomization question

Will do

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 17, 2008 3:23 PM
To: Shirley Cosby
Subject: FW: Support randomization question

Hi Shirley,

The vote is still out; waiting for Neil to chime in though so far it looks like the baby will not be counted as enrolled but PLEASE wait to take him off until we hear from Neil.

Thanks,

Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 17, 2008 4:04 PM

To: Das, Abhik; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Cc: Gantz, Marie; Poole, W. Kenneth
Subject: Re: Support randomization question

You are correct -

Neil do you agree??

Rose

Rosemary D. Higgins, MD

Program Scientist

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

From: Das, Abhik <adas@rti.org>

To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>

Cc: Gantz, Marie <mgantz@rti.org>; Poole, W. Kenneth <poo@rti.org>

Sent: Mon Nov 17 15:57:48 2008

Subject: RE: Support randomization question

Since protocol was not followed for a substantial amount of time, does

this make the research question very difficult to answer? If so, we may

not want to count this baby as having been enrolled in the trial because

randomization did not occur within the specified 2-hours window.

Thanks

Abhik

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

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

Sent: Monday, November 17, 2008 3:09 PM

To: Zaterka-Baxter, Kristin; nfiner@ucsd.edu

Cc: Das, Abhik; Gantz, Marie

Subject: RE: Support randomization question

If Neil agrees, I think the infant can be included with 2 protocol violations - CPAP not started on time and oximeter not started until XX hours of age. let me know what you think.

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]

Sent: Mon 11/17/2008 2:12 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu

Cc: Das, Abhik; Gantz, Marie

Subject: Support randomization question

HI,

UAB consented a mom a couple of weeks ago to Support; the mom delivered (b) (6) at 8:30PM but was not randomized by the respiratory team.

This was discovered by the research team at 7:30(b) (6), a

randomization card was pulled (CPAP arm) and a study oximeter was placed. The infant was place on CPAP at 0730; prior to the randomization the baby was on oxygen and not vented. In past cases we have asked that a protocol deviation be completed and the infant stayed on study but typically the randomization occurred within the 2 hour window for oximeter placement. Please advise whether this infant should remain on study or be counted as a missed case.

Thanks,

Kris

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

P.O. Box 12194

RTP, NC 27709-2194 USA

(tel) 919-485-7750

(fax) 919.485.7762

kzaterka@rti.org <mailto:kzaterka@rti.org>

www.rti.org <http://www.rti.org/>

Federal Express/UPS/DHL Shipping Address:

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

RTP, NC 27709 USA

From: Hensman, Angelita
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support infant
Date: Tuesday, November 18, 2008 1:51:14 PM

Thanks Rose. Will do.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 18, 2008 1:21 PM
To: Laptook, Abbot; nfiner@ucsd.edu
Cc: Hensman, Angelita; kzaterka@rti.org; adas@rti.org
Subject: Re: support infant

Abbot and Neil -
The study pulse ox can be discontinued due to the medical circumstances. If possible, please retain the child in the study and continue to collect data. I have talked to Kris and Abhik.
Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

From: Laptook, Abbot
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hensman, Angelita
Sent: Tue Nov 18 11:21:23 2008
Subject: support infant

Neil
Need some guidance regarding an infant in the support trial, (b) (6) who was diagnosed with a (b) (6) at some time after birth. The Cardiologists would like the range of oxygen saturations used to care for the infant from 80-88%. I don't see how we can keep the infant on the study pulse oximeter with this desired range of saturations. Does the infant come off the study pulse oximeter? Let me know, AL

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From:	Finer, Neil
To:	Walsh, Michele; alaptook@WIHRI.org; Shankaran_Seetha" <; Barbara Stoll; ambal@uab.edu
Cc:	Matt Laughon; Langer, John C.; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: PAS abstract draft for your review and comment
Date:	Friday, November 14, 2008 1:26:51 PM
Attachments:	2008 PAS Hypercarbia -NF Mods Nov 14 08.doc

Hi Michelle
I made a few corrections- mostly spelling
I think this message is important and SUPPORT will certainly shed light on this issue
I think that the high PaCO2 is probably an excellent proxy of the severity of resp disease and compromise
Do we need to use the 2 terms hypercapnia and hypercarbia? – I would stick with one and use it throughout
This is important – we need to get the manuscript out soon – I suspect that you already have it written!!
Be well
Neil

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Thursday, November 13, 2008 2:55 PM
To: alaptook@WIHRI.org; Finer, Neil; Shankaran_Seetha" <; Barbara Stoll; ambal@uab.edu
Cc: Matt Laughon; Langer, John C.; Higgins_Rosemary_" <
Subject: PAS abstract draft for your review and comment

HI All:
Attached is a near final draft of the hypercarbia abstract.
John got the analyses done by July: so any delay is my
Responsibility! These data add to Ambal and Wally's single center
That really indicates the importance of an RCT: I would support what Wally has suggested
that plan a secondary study nested within SUPPORT to look at this early impact of hypercarbia.
Appreciate your thoughts.

Michele Walsh
Medical Director NICU
Rainbow Babies & Childrens Hospital
Case Medical Center
Professor, Deparment of Pediatrics
Case Western Reserve University
phone: 216-844-3759
FAX: 216-844-3380
michele.walsh@cwru.edu
michele.walsh@UHhospitals.org (emails are interchangeable)

Title: Risk of Intraventricular Hemorrhage (IVH) is associated with exposure to hypercarbia in the first week of life.

M Walsh, JC Langer , N Finer, S Shankaran, N Ambalavanan, A Laptook, for the NICHD NRN Benchmarking Subcommittee.

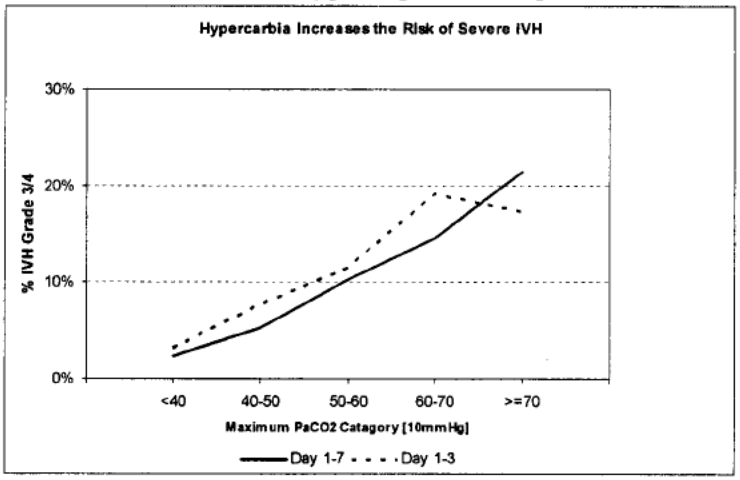
Background: Permissive hypercapnia has been proposed as a protective strategy to reduce lung injury in vulnerable preterm infants. Little is known about the safety of this strategy in the first days of life when the risk for IVH is greatest.

Objective: To examine the relationship between exposure to hypercarbia during the first 7 days of life and IVH and severe IVH (Grade 3 or 4).

Methods: 762 neonates with birthweight 501-1249 g had blood gas results (recorded at 6-hour intervals as a component of a trial of quality improvement to reduce bronchopulmonary dysplasia) and head ultrasounds Exposure to hypercarbia was calculated as maximum CO2 and cumulative exposure to CO2. The relationship between exposure to hypercarbia, and IVH was examined with univariate and logistic regression analyses with IVH as a categorical variable (none, mild, severe) adjusted for gestational age, antenatal steroid exposure, male gender, c-section, 5m Apgar <=3, Lowest Temp 1st 12 hrs, pneumothorax and severity of illness (SNAP score at 12 hours).

Results: 530 of 762 infants (bwt 898 ± 207; GA 26.9 ± 2.2 wk) had no IVH and 232 (36%) had IVH (Grade 1-2, n= 143; Grade 3-4, n=89). Infants with IVH were smaller, less mature, less likely to have antenatal steroids, male, hispanic, and received more delivery room resuscitation. After adjustment, elevations of CO2 in the first 3 and first 7 days of life remained significantly associated with any IVH and severe IVH. All measures of CO2 elevation were associated with increasing risk: maximum CO2, cumulative exposure to CO2, and any CO2 > 50 mmHg. For any PaCO2 above 50 mmHg the risk of any IVH increased (OR 1.484 (0.996-2.211) and severe IVH increased. (OR =2.064 (1.017-4.188). In addition, the risk for Grade 1 or 2 IVH was also increased.

Conclusions: Hypercarbia in the first 7 days of life increased the risk of any IVH and severe IVH. Early permissive hypercapnia strategies should be used with caution.



From: Finer, Neil
To: Walsh, Michele; Julie Di Fiore; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Martin, Richard; Wally_Carlo_M.D." <
Subject: RE: Draft of Desat vs ROP abstract
Date: Friday, November 14, 2008 1:06:32 PM

This looks very interesting and NO I should not be a part of this as I don't think we provided any data.
Nice work Julie!!
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Thursday, November 13, 2008 3:34 PM
To: Julie Di Fiore; Higgins_Rosemary_" <
Cc: Martin, Richard; Finer, Neil; Wally_Carlo_M.D." <
Subject: RE: Draft of Desat vs ROP abstract

Hi Rose: I want to run this by you.

As you know we have been doing a desat secondary analysis

Within SUPPORT. In parallel with this NRN secondary study, we have also been

Tracking babes of the same GA who were NOT enrolled in SUPPORT.

The data are intriguing, and suggest a method that may be productive

For analyzing the SUPPORT data in the future. Wanted you all to see this

In advance of the PAS meeting submissions. Be well,

Michele Walsh

<<DiFiore Abstract Desaturations.doc>>

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: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz
Subject: RE: School Age Pulmonary Follow up Proposal
Date: Monday, November 10, 2008 12:50:41 PM

I think Richard would do a good job of briefly reviewing the protocol
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 10, 2008 6:59 AM
To: Finer, Neil; Susan Hintz
Subject: FW: School Age Pulmonary Follow up Proposal

Can you let me know if you want Richard on the first few minutes of the call to discuss this protocol?
Thanks
Rose

-----Original Message-----
From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Wednesday, November 05, 2008 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: School Age Pulmonary Follow up Proposal

Rose:
Should I participate in this call?
Richard

Higgins, Rosemary (NIH/NICHD) [E] wrote:
> We are setting up a call for the SUPPORT subcommittee to discuss (will occur 12/3). If the subcommittee is in favor, then a cocnept can be presented at the Jan 8-9 meeting.
> Thanks
> Rose
>
> ----- Original Message -----
> From: Richard Ehrenkranz <richard.ehrenkranz@yale.edu>
> To: Stevens, Timothy <Timothy_Stevens@URMC.Rochester.edu>
> Cc: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Tue Nov 04 17:33:54 2008
> Subject: Re: School Age Pulmonary Follow up Proposal
>
> Tim:
> I spoke with Neil in October and asked him to submit it to the SUPPORT
> subcommittee. With there approval, I think it should be submitted as a
> concept for the January Steering Committee; therefore, I have copied

> Rose on this response.
> Richard
>
> Stevens, Timothy wrote:
>
>> Hi Richard and Neil,
>>
>> Have you had a chance to judge the enthusiasm for a school age pulmonary outcome study as a follow up to SUPPORT and Breathing Outcomes?
>>
>> Rose recently wrote that there are concept proposal slots open for January's meeting. So if there is interest, perhaps we could aim for presenting the idea at that time.
>>
>> Attached is the proposal with Richard's suggestions incorporated.
>>
>> Thanks
>>
>> Tim
>>
>>
>> -----Original Message-----
>> From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
>> Sent: Monday, September 29, 2008 1:04 PM
>> To: Stevens, Timothy
>> Cc: nfiner@ucsd.edu
>> Subject: Re: School Age Pulmonary Follow up Proposal
>>
>> Tim:
>> I thought that this protocol was great. I had several minor
>> edits/comments [I have highlighted # 1 and 2]:
>>
>> 1. Page 5, line 6 Insert the word "and".
>> 2. Page 8, line 3: A phrase is missing.
>> 3. Appendix 2, page 11: Why did the total N change to 381 from 384?
>>
>> Otherwise, I think that it should be presented to the SUPPORT
>> subcommittee for review. What do you think Neil?
>> Richard
>>
>> Stevens, Timothy wrote:
>>
>>
>>> Hi Richard and Neil,
>>>
>>> Attached is a first draft of a proposal entitled, SUPPORT - School Age
>>> Breathing Outcomes Study. The goals of the proposal are to determine
>>> whether the pulmonary effects of SUPPORT are sustained to school age
>>> by measuring pulmonary function of SUPPORT patients at 6-7 years of
>>> age. As a major secondary goal, the proposal describes studies to
>>> determine whether the pulmonary benefits of SUPPORT reduce reaction or
>>> susceptibility to secondary pulmonary insults such as environmental
>>> tobacco smoke, infections and inhaled allergens during childhood.
>>> Together these goals have potential to substantially increase our
>>> understanding of pulmonary morbidity among extremely preterm infants.
>>>
>>> Please let me know your thoughts.
>>>

>>> Thanks
>>>
>>> Tim Stevens
>>>
>>> Timothy P. Stevens, MD, MPH
>>>
>>> Associate Professor of Pediatrics (Neonatology)
>>>
>>> Medical Director, NICU
>>>
>>> Golisano Children's Hospital at Strong
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>>> University of Rochester, Box 651
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>>> Rochester, NY 14642
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>>> 'phone: (585) 275-2972 7fax: (585) 461-3614
>>>
>>> æpage: (585) 275-(b) (6)beeper#(b) (6)
>>>
>>> : email: timothy_stevens@urmc.rochester.edu
>>>
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>

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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

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; srhintz@stanford.edu
Cc: adas@rti.org; vanmeurs@leland.stanford.edu; mbball@leland.stanford.edu; kzaterka@rti.org
Subject: RE: Please call - weird question about SUPPORT
Date: Friday, November 07, 2008 4:10:11 PM

I agree with Rose
Neil
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 07, 2008 9:23 AM
To: srhintz@stanford.edu
Cc: Finer, Neil; adas@rti.org; vanmeurs@leland.stanford.edu; mbball@leland.stanford.edu; kzaterka@rti.org
Subject: Re: Please call - weird question about SUPPORT

I talked to Susan and told her to treat this as a separate case (even though (b) (6)) if they obtain consent (I.E. New randomization)..

If you have any other input, hit reply all and explain.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Susan Hintz <srhintz@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 07 12:16:16 2008
Subject: Please call - weird question about SUPPORT

Hi Rose,

If you get this - I know you are out of the office - please give me a call on my cell 650-799(b) (6). we have a mother in preterm labor at 24 weeks who we are planning to approach for SUPPORT - BUT, (b) (6) (yes, bizarre but true). So, my question is whether this issue has been raised previously, whether randomization should be considered the SAME as if this is a totally separate patient, or whether it is even appropriate to approach this woman (b) (6) ...stacking the deck a bit?)

I also left a message for Abhik

Susan
--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine

750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; srhintz@stanford.edu
Cc: nfiner@ucsd.edu; vanmeurs@leland.stanford.edu; mbball@leland.stanford.edu; Zaterka-Baxter, Kristin
Subject: RE: Please call - weird question about SUPPORT
Date: Friday, November 07, 2008 12:24:36 PM

Susan:

Please send us the id's for the (b) (6) (once you enroll this baby) because we still want to keep track of this. I guess the mom needs to understand that this baby may end up in a different treatment group than (b) (6)

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 07, 2008 12:23 PM
To: srhintz@stanford.edu
Cc: nfiner@ucsd.edu; Das, Abhik; vanmeurs@leland.stanford.edu; mbball@leland.stanford.edu; Zaterka-Baxter, Kristin
Subject: Re: Please call - weird question about SUPPORT

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If you have any other input, hit reply all and explain.

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist

----- Original Message -----
From: Susan Hintz <srhintz@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 07 12:16:16 2008
Subject: Please call - weird question about SUPPORT

Hi Rose,

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I also left a message for Abhik

Susan
--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine Stanford University
School of Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

From: Wally Carlo, M.D.
To: Webb, Robin E.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; nfiner@pedsmail.ucsd.edu
Subject: RE: SUPPORT - School Age Breathing Outcomes Proposal 9-12-08
Date: Wednesday, November 05, 2008 7:07:51 PM

Robin:

I will be out of the country this day.

Neil/Rose:

I am concerned that we are planning a school age outcome before knowing whether 2 year outcomes are improved. If not improved at 2 years, I would not favor a later FU.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Tuesday, November 04, 2008 8:35 AM
To: Webb, Robin E.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo, M.D.; mcw3@cwru.edu; Bradley.yoder@hsc.utah.edu; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie; Susan Hintz; Poole, W. Kenneth
Cc: Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Huitema, Carolyn Petrie; Newman, Jamie; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; bvecchio@careNE.org; Marsha Sumner; fmartinez@ucsd.edu
Subject: SUPPORT - School Age Breathing Outcomes Proposal 9-12-08

The call to discuss the proposal for school age breathing outcomes has been scheduled for:

Tuesday, 12/2
3:00pm ET

Dial:
Within the USA
866-675(b) (6)

or

Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6) #

From: Katherine A Foy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Thursday, October 30, 2008 1:52:07 PM

CENTER NETWORK ROP_message

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.- window is open

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.- corrected

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.- corrected

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.- corrected

CENTER NETWORK BPD_message

19 (b) (6) Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing- we are in the process of getting the information

CENTER NETWORK FU_message

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed-visit completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed-scheduling 18 month visit.

Kathy Foy, RN
Clinical Research Coordinator
Duke University Health Systems
Neonatology
681-5859 office
970-1421 pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> To "Ronald GOldberg" <goldb008@mc.duke.edu>, <golds005@mc.duke.edu>,

10/22/2008 04:28 PM
<foy00004@mc.duke.edu>, <Kimberley.fisher@Duke.edu>, <lohme001@mc.duke.edu>, <cotte010@mc.duke.edu>

cc

"Das, Abhik" <adas@rti.org>, "Marie Gantz" <mgantz@rti.org>

Subject

SUPPORT

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER NETWORK ROP_message

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.

CENTER NETWORK BPD_message

19 (b) (6) Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

CENTER NETWORK FU_message

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: Das, Abhik; Marie Gantz
Subject: RE: SUPPORT OUTCOMES
Date: Monday, October 27, 2008 5:31:25 PM

(b) (6) – incorrect data entered and has been fixed.
(b) (6) – had one follow up eye exam done after discharge, still immature and missed other appts thereafter. Will call eye doctor to see if patient came back recently.
(b) (6) – finally saw this child last week after multiple rescheduled appts! Forms have been entered today in the computer.
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 3:22 PM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.
GIVEN THE OUTSTANDING RECRUITMENT, THIS IS PHENOMENAL!!!!
Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
16	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: karen-johnson@uiowa.edu; edward-bell@uiowa.edu; adas@rti.org; kristin zaterka
Subject: Re: Iowa and IRB and SUPPORT FU
Date: Friday, October 24, 2008 3:09:31 PM
Attachments: Follow6_7yearNeuroSUPPORT033008 copy.doc
MockPatientTrackContactsSUPPORT6_7year.doc
MockSiteTrackingListSUPPORT6_7year.xls

Hi all,

Attached is the protocol - This will at least detail the timing of visit (which will not change), the hypotheses for the study (which will not change) and the *general* tests and instruments for assessment that will occur at 6-7 year visit. Also in the protocol is the *reasoning for need to begin tracking* - that might help.

The COGNITIVE instrument (i.e., IQ test) will not be the WPPSI for the reasons I discussed that the Steering Committee meeting, but it will still be AN IQ TEST, so really not that different.

I am not sure that we should send tracking forms since they have not been distributed yet by RTI. Can we not say that patients enrolled in the Neuroimaging and Neurodevelopmental outcome study will be asked for their consent to continue contact...and that's it?

Thanks and let me know. I attached the tracking form drafts (and Abhik has them too) just in case some version is needed - the "mock patient track contacts" is a tool for sites to gather contact information for each patient. the "mock site tracking list" is a tool for each site to have their ENTIRE list of patients and running information about contacts.

Susan

Susan R. Hintz, M.D., M.S. Epi
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Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

> Susan
>
> Karen Johnson needs a simple explanation of why we are going to keep in contact with the Support children. Can you send her the protocol draft and the tracking forms. She will write a few paragraphs and this should suffice with her IRB. She won't submit the protocol to the IRB
>
> Thanks
> Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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--

Extended follow-up at 6-7 years of age of patients enrolled in the Neuroimaging and Neurodevelopmental Outcome Secondary to SUPPORT

Subcommittee:

Susan Hintz, M.D., M.S. Epi.
Betty Vohr, M.D.
Maureen Hack, M.D.
Neil Finer, M.D.
W. Kenneth Poole, Ph. D.
Jane Hammond, Ph.D.
Abhik Das, Ph.D.
Seetha Shankaran, M.D.
M. Bethany Ball
Rosemary Higgins, M.D.

I) ABSTRACT:

The NICHD NRN SUPPORT Neuroimaging cohort will be the largest cohort of extremely preterm infants with brain magnetic resonance imaging (MRI). Children born extremely prematurely continue to have significant neurodevelopmental challenges in later childhood; many subtle yet significant cognitive and performance problems cannot be delineated until 5-8 years and beyond. Early and accurate prediction of neurodevelopmental outcome would be invaluable, but cranial ultrasound (CUS) and other early variables do not reliably predict outcomes. White matter (WM) injury has been strongly implicated in both neuromotor and cognitive impairment, and a developmental neuroanatomical link between WM injury and gray matter disruption appears to exist. MRI is better than CUS in identifying subtle and diffuse WM injury, as well as cerebellar, and gray matter abnormalities. Small and larger studies to date, including the 2-year New Zealand premie MRI cohort results, have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities. But a significant association of MRI abnormalities with cognitive impairment at 18-24 months has not yet been reported. However, subtle neonatal MRI abnormalities may predict cognitive problems in early school age that cannot be delineated in very early childhood. Death after discharge is a competing outcome for outcome at 6-7 years. **Therefore, we propose a 6-7 year neurodevelopmental follow-up of the SUPPORT Neuroimaging cohort to test the hypothesis that neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment and disability at 6-7 years. We will also assess whether injury severity on neonatal MRI will be associated with longitudinal cognitive and disability level changes. In addition, we will examine cognitive impairment and disability between ventilatory or oxygenation saturation SUPPORT intervention groups.** The SUPPORT Neuroimaging cohort is valuable and unique among other worldwide premie MRI cohorts; by undertaking 6-7 year follow-up, the NICHD NRN is in an outstanding position to substantially contribute to the understanding of the later outcomes of extremely preterm infants and their prediction.

Hypotheses: Among <28-week EGA children enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary, surviving to hospital discharge:

PRIMARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment (WPPSI-III IQ<70) at 6-7 years

SECONDARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment (WPPSI-III IQ<70) at 6-7 years
- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or disability at 6-7 years
- Neonatal brain MRI will be superior to neonatal CUS in predicting disability at 6-7 years
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the frequency of death after discharge or cognitive impairment, disability,

or cerebral palsy between ventilatory or oxygenation saturation SUPPORT intervention groups in this sub-cohort.

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or CP at 6-7 years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting CP at 6-7 years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting mild-moderate cognitive impairment (WPPSI-III 1-2 SD below population mean) at 6-7 years
- Local readings of neonatal MRI will be less predictive of 6-7 year outcomes than central reading
- Compared to central reading, local readings of both neonatal CUS and MRI will moderately to highly accurate for overall abnormal or severely abnormal findings, but poorly accurate for subtle findings.
- Injury severity and pattern on neonatal MRI will be associated with longitudinal cognitive and disability level changes
- Brain injury pattern and topography on neonatal MRI will be associated with anatomic and functional type of CP

Specific Aims:

- To assess cognitive, neuromotor, functional and behavioral outcomes of the SUPPORT Neuroimaging cohort at 6-7 years of age
- To examine the independent associations of neonatal neuroimaging findings with neurodevelopmental outcomes
    - Assess the absolute and relative value of early and late neonatal CUS and neonatal MRI, alone and in combination with other risk factors, to predict normal and impaired outcomes
- To examine longitudinal changes in cognitive and overall impairment level from 18-22 month to 6-7 year exams, and assess relationship of neonatal neuroimaging abnormalities and other variables.
- To compare 6-7 year neurodevelopmental outcomes of ventilation and oxygenation SUPPORT randomized groups in this sub-cohort.

II) BACKGROUND AND SIGNIFICANCE:

Long-term neurodevelopmental outcomes of extremely preterm infants:

Despite advances in perinatal and neonatal management and improvement in survival, short-term neurodevelopmental outcomes of extremely preterm and extremely low birth weight (ELBW) infants appear to remain guarded (Vohr, Hintz, Costeloe). This reported high frequency of disability in very early childhood (18-24 months) makes longer-term neurodevelopmental outcome studies crucial. Evaluation at a later age allows identification and delineation of a broader range of problems, including cognitive delay, more subtle motor disabilities, and behavioral problems to be determined. It also allows for assessment of the strength of perinatal and neonatal variables as potential predictors of long-term outcome, and for longitudinal analysis to determine the predictive value of early disability.

Later childhood follow-up studies have demonstrated that significant neurodevelopmental and cognitive impairment continue. In the 206 ELBW infants

followed at 5 years in the Finnish National Cohort (Mikkola), 20% had major disabilities, and 19% of those <27 weeks were diagnosed with cerebral palsy (CP). The EPICure Study Group (Marlow) reported on 241 <26 week survivors at 6 years; severe overall cognitive delay was present in 21% compared with test norms (41% compared with term controls), and disabling CP was diagnosed in 13%. In a study of 219 ELBW infants 8 years (Hack), Hack, et. al. reported CP in 14%, severe cognitive impairment in 15%, moderate-severe cognitive impairment in 38%, and significant motor skills problems in 27%. Families reported substantial functional limitations, including emotional delay, trouble understanding or communicating, and need for medication or equipment; needs for special services were significantly greater than for the normal birth weight (NBW) control group. Impairment in academic (32%) and adaptive skills (48%) have also been reported among ELBW children, and are significantly more frequent than in NBW controls (Taylor). In an ELBW or <28 week EGA cohort at 8 years (n=275), Anderson, et. al. reported significant impairment across all tested cognitive and educational abilities compared with NBW controls (Anderson).

Summary: Children born extremely preterm or ELBW continue to have substantial motor and cognitive disabilities in childhood, as well as more subtle functional and adaptive impairments. Delineation of some of these problems may not even be reasonably undertaken until 5-8 years of age. The true impact of these impairments may not be felt until later school age (Saigal).

Predicting neurodevelopmental outcome: Neonatal CUS and other variables:

CUS and short-term (18-24 months)

The association of a combination of severe neonatal CUS abnormalities and adverse short-term neurodevelopmental outcome has been reported in numerous studies (Vohr, Hack#2). But, even in the most detailed CUS studies, the strength of this association appears to be consistent primarily for combined endpoints, or for CP or motor disability, but not for pure cognitive delay (deVries, Hack #2, Wood). In addition, severe CUS abnormalities are not uniformly predictive of adverse short-term outcome and normal CUS do not predict normal outcome in this high-risk population (deVries, Hack#2, Laptook, Ancel, Pinto-Martin). In fact, in a predictive modeling analysis, Ambalavanan found that severe grade of IVH explained only 8% of the variance in low MDI and 5% of the variance for major handicap at 18-22 months (Ambalavanan).

CUS and long-term outcome (5-8 years)

Reported associations of neonatal CUS findings and long-term outcomes are inconsistent. Sherlock, et. al. (Sherlock) reported that neurodevelopmental impairment at 8 years varied little with increasing severity of IVH; a trend for worse cognitive and neurosensory outcome with higher grade IVH explained solely by the outcomes of the small number of patients with parenchymal hemorrhage. Similarly, 6-year results of the Neonatal Brain Hemorrhage Study (NBHS) showed that 88% of LBW patients with germinal matrix or IVH had normal cognitive outcomes (Whitaker).

Nevertheless, several analyses have reported abnormal neonatal CUS to be "significantly associated with" adverse long-term neurodevelopmental outcomes in ELBW cohorts. For instance, Mikkola found an association of abnormal CUS with CP and IQ at 5 years (Mikkola), and Taylor found an association of abnormal CUS with

executive function and memory on the NEPSY (Taylor). However, the definition of CUS "abnormality" varies among studies, with some analyses including markers of white matter injury (PVL or ventricular enlargement (VE)) and others limiting only to IVH. In addition, a finding of association does not specifically address the independent *predictive* power of neonatal CUS, particularly with respect to cognitive outcome in later childhood. In fact, Hack, et. al. demonstrated that only 36% of those with a Mental Processing Composite (MPC) of <85 at 8 years had had an abnormal CUS, and only 45% of those with MPC<70 (Hack #3). In the 6-year follow-up of the NBHS cohort, only 12% of those with GM/IVH had borderline IQ or mental retardation (Whitaker). In that study, PVL/VE was separately assessed; this revealed a stronger 56.5% of those with PVL/VE had borderline IQ or mental retardation. This may be a clinical insight to the importance of white matter (WM) injury for longer-term adverse outcomes *including cognitive outcomes*. Nevertheless, more that 40% of patients with PVL/VE had normal intelligence at 6 years - a finding, which, in turn, may serve to underscore the inability of routine CUS to see anything more subtle than the most definitive WM injury.

Other potential predictors of long-term neurodevelopmental outcome:

Investigators have attempted to determine other, more reliable predictors of longer-term outcomes of preterm infants. Doyle reported on prediction of survival free of major disability at 5 years among the surviving VICS cohort on the basis of the number of "adverse neonatal variables" (Doyle #2). Although observed and predicted values were similar, the outcome was not specifically focused (i.e., combined neurologic/neurosensory/cognitive endpoint), the observed 95% CI range was broad for 2 and 3 variable groups, and the patient numbers were quite small. Others have assessed the predictive value of *earlier neurodevelopmental findings*. Marlow found that only severe disability at 30 months was highly predictive of 6-year outcome; 38% of children defined as mild or moderately disabled and 24% with "no disabilities" had moderate or severe disabilities at 6 years. Hack (#3) found the positive predictive value of MDI<70 at 20 months for MPC<70 at 8 years to be extremely poor (PPV=0.37). However, some intriguing links of longitudinal decline in cognitive ability with brain injury have been reported. In follow-up to the I-IVHP trial, Ment found that cognitive scores declined from 36 to 96 months only in the subset of patients with early IVH coupled with PVL or VE (Ment). Also from the I-IVHP trial, the presence of spastic cerebral palsy at 3 years was more strongly predictive of IQ<70 at 8 years than was cognitive testing at 3 years (Pleacher). These findings are not surprising, in part due to the potential mechanism linking white matter injury with reduced connectivity, gray matter loss, and cognitive delay.

Summary: Aggregate abnormal findings on neonatal CUS do not reliably predict either short- or long-term neurodevelopmental outcomes, although markers of WM injury appear to be stronger links. Early cognitive measures also do not predict later cognitive outcome well in most circumstances. These findings emphasize the deficits of routine CUS to detect subtle injury, and also underscore the poor predictive validity of early cognitive measures for later cognitive outcomes (Aylward).

MRI: Delineation of injury and predicting outcomes

Imaging injury:

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Studies comparing the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period have concluded that MRI detects white matter injury better than CUS (Maaloof, Childs), and provides additional information on brain development not noted by cranial US. Studies have also demonstrated that subtle and diffuse WM injury, not detectable by CUS, may be common among preterm infants at term (Counsell).

White matter injury and cognitive outcome:

Cognitive delay is a significant and difficult to predict component of the range of impairments. Recent studies have demonstrated that white matter injury in the preterm infant is associated with both reduced cortical gray matter volume, and with reduced deep gray matter volume by MRI at term equivalent age (Inder, Boardman). There are several potential mechanistic pathways, including via direct axonal or subplate neuron injury that may explain this finding. The common endpoint is reduced connectivity, limited neuronal differentiation, and poor cognitive outcome. In fact, recent research using MRI tractography in a series of former preterm infants at approximately 2 years of age has provided evidence for this theory of reduced cortical and thalamic connections after WM injury (#2 Counsell).

MRI in preterm infants and early neurodevelopmental outcome

After early studies suggesting that MRI at near term was a more powerful predictive tool than CUS for short-term neurodevelopmental outcome (Valkama, Roelents-van-Rijn, Mirmiran), larger MRI studies were undertaken. Many have been single-center efforts, focused chiefly on the association of early neurodevelopmental outcomes with MRI findings in preterm infants at term and earlier, and without extensive comparison of the predictive validity of MRI and CUS. Among these, Miller, et. al. (UCSF, <34 weeks EGA, 86 survivors) and Dyet, et. al. (Hammersmith, <30 weeks EGA, 119 survivors) described MRI findings from birth through near-term and found that WM injury, particularly diffuse injury, was common and was associated with adverse neurodevelopmental outcomes. Cerebellar injury, not easily seen with routine CUS, was also a prognostic indicator of poor outcome. Of importance, although MRI data were meticulously obtained, only 66% of the group had complete follow-up data.

However, other groups have preterm/MRI cohorts, with research aims that include comparison of predictive capabilities of MRI and CUS.

- The recently reported 2-year neurodevelopmental outcomes of the New Zealand (NZ) cohort (Woodward) (<30 weeks EGA, 167 survivors) revealed that 1) presence of moderate-severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) although increasing severity of WM injury was associated with worse Bayley MDI scores, an independent association of moderate-severe WM injury with severe cognitive delay was not reached. Although sensitivity of moderate-severe WM to predict CP (65%), neurosensory impairment (82%) and severe cognitive delay (41%) was improved over abnormalities on CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n=29) or severe (n=6) WM injury was small, and approximately half of those did not have neurodevelopmental impairment.

- The 2-years results of the Australian cohort (<1250 g or <30 weeks EGA, n=221) were reported at the 2007 PAS (Hunt). "Major" white matter injury was found to be a more significant independent risk factor than PVL for CP, and was an independent risk factor for neurosensory disability where PVL was not. IVH grade 4 was not found to be a significant risk factor for either outcome.
- **SUPPORT Neuroimaging cohort:** Continuing enrollment; first enrolled birth date 5/10/05. Follow-up at 18-22 months ongoing.

SUPPORT Neuroimaging cohort: Unique and valuable

The SUPPORT Neuroimaging cohort, estimated to include 400-450 survivors with complete CUS and MRI data by the time SUPPORT enrollment closes, will be the largest preterm/MRI/follow-up cohort worldwide. This cohort is also a higher-risk group than other cohorts, and thus innately targets the most important outcomes group. Follow-up at 18-22 months is in progress, with the first enrolled SUPPORT Neuroimaging patient follow-up window 2/6/07-6/21/07. The SUPPORT Neuroimaging cohort is inherently exceptional and unique in that it was developed within a randomized controlled trial. Thus, the management profile of a crucial neonatal care component has been more carefully controlled and monitored than would otherwise be the case. This also allows for secondary analyses of the association of respiratory management strategies with subtle MRI findings and outcome. The SUPPORT Neuroimaging cohort also has a number of advantages over other preterm/MRI cohorts:

1) New Zealand (NZ) cohort:
    a. Setting: SUPPORT: Embedded in a randomized controlled trial within a multicenter network with focused neurodevelopmental follow-up priorities; NZ: two centers one in New Zealand another in Melbourne, Australia, with a primary focus on MRI imaging
    b. EGA/risk profile:
        i. SUPPORT: <28 weeks EGA; NZ cohort: <30 weeks. Only 87/167 of the NZ cohort was <1000 g BW, and 95/167 were <28 weeks.
    c. Cohort size: SUPPORT: estimated 400-450 survivors; NZ: 167 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. SUPPORT: Two specifically-timed and required CUS, including near-term; NZ: within 2 days, 5-7 days, 4-6 weeks; if "abnormality" detected, more frequent performed.
        ii. SUPPORT: central reader, detailed central reader data instrument; NZ: No central reader. "Worst" CUS findings recorded only with respect to PVL/echolucency, grade 3 or 4 IVH
    e. Timing/interpretation of MRI:
        i. BOTH: Near-term
        ii. BOTH: Central reader
        iii. SUPPORT: detailed MRI central reader form; NZ: central reader data collection instrument not known, but MRI abnormality categories broad.
    f. Non-imaging data collection:
        i. SUPPORT: extensive, including detailed respiratory data; NZ: less detailed

2) Australia cohort:
    a. Setting: Single center in Melbourne, Australia
    b. EGA/risk profile:
        i. <30 weeks, <1250 g.
    c. Cohort size: 221 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. Not required, retrospectively gather information (communication, Rod Hunt).
        ii. "Worst" CUS findings gathered - PVL, grade 4 IVH
    e. Timing/interpretation of MRI:
        i. Near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
3) Hammersmith cohort:
    a. Setting: Single center
    b. EGA/risk profile:
        i. <30 weeks.
    c. Cohort size: 119 survivors at 2 years. **Note: complete follow-up data were available for only 66% of the group**
    d. Timing/interpretation of CUS:
        i. CUS not focus – studies thus far report MRI
    e. Timing/interpretation of MRI:
        i. MRI serial – from birth to near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
4) UCSF:
    a. Small, single center
    b. <34 weeks
    c. 86 survivors at 2 years
    d. CUS not focus – MRI's serial from birth to near-term
    e. Non-imaging data routine

Summary: MRI is better than CUS in identifying subtle and diffuse white matter injury, which is relatively common among preterm infants at term, as well as cerebellar, and gray matter abnormalities. Earlier small studies suggested that MRI better predicts adverse neuromotor outcome than CUS. Two-year results of the NZ cohort have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities, but not with adverse cognitive outcome. The extent to which these findings will be enhanced and clarified, and how or when MRI should be applied in routine clinical practice, awaits the 18-22 month results of the larger, higher-risk SUPPORT Neuroimaging cohort. However, a biologic mechanism for the link between WM injury and cognitive impairment exists. Early cognitive findings are poor predictors of later challenges, and subtle neonatal MRI abnormalities may predict subtle problems in early school-age that cannot be delineated at 18-22 months.

Later outcomes: Need for SUPPORT Neuroimaging extended follow-up

Evidence for altered brain development: corroboration of need for long-term follow-up

Short-term neurodevelopmental outcomes are only a tiny window into the future of a former preterm child. Difficulties in cognition, performance, verbal/language skills, attention and behavior may not be delineated until later ages. There are also data to support the concept that even minor, undiagnosed brain injury sustained preterm infant is associated with disordered brain development. The degree of white matter injury purported to be associated with reduced connectivity and subsequent gray matter reduction may be subtle, and its effects dependent on other variables (Inder, Boardman). Rademaker, et. al. found that even minor differences in lesion severity on MRI performed at 8 years of age in <32 week EGA appeared more accurate in prediction of IQ and total impairment score than neonatal CUS (Rademaker). These findings may suggest that subtle injury could have been seen on *neonatal* MRI, which in turn, could have aided in prediction. In a DTI and volumetric MRI study, Yung demonstrated that *neurologically normal* LBW preterm infants at 8-12 years had significantly reduced WM volumes than term controls, and that this was significantly related to reduced IQ (Yung). This finding again suggests that early WM injury leading to reduced volume may have been identifiable on neonatal MRI. Kesler, et. al. described high-resolution MRI results from 73 preterm and 33 term infants at 7-11 years of age; preterm infants had disorganized cortical development, potentially involving disrupted neural migration (Kesler).

Importance of SUPPORT Neuroimaging secondary long-term follow-up

The importance of long-term follow-up for any preterm cohort with neonatal MRI's is clear.

- Our current ability to predict later childhood outcomes from perinatal and neonatal variables is limited. The prognostic validity of neonatal CUS findings is limited. Even early childhood neurodevelopmental outcome, apart from severe impairment, do not accurately predict later childhood neurocognitive outcome. MRI holds promise as a better predictive modality, but neonatal MRI has not been evaluated with respect to truly long-term outcomes.
- Performance skills are different at 18-22 months than 6-7 years; assessments at the later age may uncover subtle, yet significant problems, which may be associated brain injury seen by neonatal MRI.
    - Such assessments may reveal attention/behavior problems, language and verbal delays, more detailed picture of cognitive/academic impairment.

But the **SUPPORT Neuroimaging cohort is unique among other cohorts, and is in an outstanding position to substantially contribute to the understanding of neonatal imaging and prediction of long-term neurodevelopmental outcomes**:

- SUPPORT Neuroimaging secondary designed with MRI/CUS predictive comparison in mind, thus careful attention to specifically-timed CUS, detailed central reading of all study neuroimaging
- 18-22 month follow-up is already part of this secondary study

  - Thus, crucial opportunity to evaluate longitudinal changes, and importantly, brain injury patterns or other variables associated with changes in cognitive or functional outcomes
- Prospectively enrolled secondary cohort, embedded within SUPPORT RCT; more consistent management of respiratory approach, comprehensive data collection
  - Opportunity for secondary analyses of randomized ventilation/oxygenation arms of Neuroimaging cohort outcomes at 6-7 years
- Study within the NICHD NRN; neurodevelopmental follow-up is already a focused objective, and follow-up rates have been outstanding for previous trials (Shankaran)
- SUPPORT cohort will be the largest and highest-risk cohort of premature infants with CUS and MRI. Much has already been invested in this valuable cohort.

In addition, it is important to recognize that other preterm/MRI cohorts, notably the NZ cohort, already have protocols in place for long-term follow-up. The NZ cohort 4-5 year follow-up is underway (communication, TE Inder).

Why we can't wait to commit to 6-7 year follow-up:

Finally, it may appear premature to plan for 6-7 year follow-up of this sub-cohort within a RCT that is still enrolling. It may seem reasonable to wait to assess 18-22 month outcome results, and commit to follow-up only after that point. But that approach will not be possible. The birth date of the first SUPPORT Neuroimaging subject was 5/10/2005. If current enrollment rate continues, SUPPORT enrollment will not likely be completed until early 2009. Thus, in the best possible scenario, the final SUPPORT Neuroimaging subject would have an 18-22 month follow-up window *opening* in early 2011, while the first SUPPORT Neuroimaging subject will reach the 6th birthday on 5/10/2011. **Therefore, analysis would not be complete for 18-22 month outcomes soon enough to allow for 6-7 year follow-up tracking, planning and preparation.**

III) STUDY DESIGN:

Objective: This is a proposed prospective follow-up study of the 6-7 year neurodevelopmental outcomes of the SUPPORT Neuroimaging Secondary cohort. We will evaluate and compare the capabilities of *neonatal neuroimaging* - CUS and near-term MRI – to predict cognitive impairment, disability, and neuromotor impairment at 6-7 years. We will evaluate longitudinal changes in neurodevelopmental outcome, and assess associated neuroimaging findings and other variables. We will also determine if ventilatory or oxygenation saturation SUPPORT interventions are associated with differences in 6-7 year neurodevelopmental outcomes.

Outcomes:

- Primary:
  - IQ by WPPSI-III<70
    - Because death after discharge is a competing outcome, the primary outcome will be WPPSI-III<70 *or* death after discharge
- Secondary:

- IQ score (continuous) by WPPSI-III
- Disability
  - Severe: Any of: WPPSI IQ >3 SD below mean, severely impaired neuromotor/functional outcome (non-ambulatory, GMFCS level 4-5), profound hearing loss or blindness (not functionally correctable),
  - Moderate: Any of: WPPSI IQ 2-3 SD below mean, moderately impaired neuromotor/functional outcome
  - Mild: Any of: WPPSI IQ 1-2 SD below mean, mildly impaired neuromotor/functional outcome (abnormal neurologic exam, but walking independently, GMFCS level 1-2)
- Cerebral palsy
  - Classified anatomically and functionally according to Definition and Classification of Cerebral Palsy, April 2006 guidelines
- Mild cognitive impairment (WPPSI IQ 1-2 SD below mean) and severe cognitive impairment (WPPSI IQ>3 SD below mean)
- Behavioral and attention deficits
- Chronic conditions and functional limitations

Study population:

- The study population (SUPPORT Neuroimaging cohort) will be comprised of the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary enrollees who survived to discharge. **By the time SUPPORT enrollment in completed, it is estimated that 400-450 infants will be in the SUPPORT Neuroimaging cohort.**
- As described in the SUPPORT Neuroimaging and Neurodevelopmental outcome secondary, these patients will have had two CUS (early: 4-14 days of age; late: 35-42 weeks and within 5 days of MRI) and a brain MRI at 35-42 weeks.
  - The CUS with the most severe abnormalities (the "worst" CUS) will be used in comparative analyses
- Estimated cohort size at neurodevelopmental follow-up
  - Follow-up at 18-22 months (ongoing)
    - Estimate 2% death after discharge, 10% loss to F-U: **cohort=350-397 pts**
  - Follow-up at 6-7 years
    - Estimate additional 10% loss to F-U: **cohort = 315-357 pts**

Design:

- This proposed protocol concept is a long-term cognitive, neurologic, and functional follow-up of the SUPPORT Neuroimaging Cohort. **No further neuroimaging is being proposed**.
- <u>Visit at 6-7 years</u>:
  - Neurologic exam and Gross Motor Function exam
    - Diagnosis of CP, type (anatomic description), and severity (Rosenbaum);
    - Gross Motor Function Classification level
    - Fine motor assessment
  - Weschsler Preschool and Primary Scale of Intelligence- III

- NEPSY
- ** Pediatric Evaluation of Disability Inventory (PEDI)**
  - For children unable to be tested by the WPPSI and NEPSY due to severe neurodevelopmental impairment
- Medical history
- Socioeconomic status (SES)
  - SES data will be assessed by a questionnaire that parallels that of the 18-22 month visit and baseline.
- Questionnaire for Identifying Children with Chronic Conditions (QUICCC)
- Attention/behavior instruments:
  - Child Behavior Checklist (CBCL)
  - Conners' Rating Scale
- Impact on Family questionnaire

Statistical considerations:
Analyses:

- Since we are concerned with the relative diagnostic power of the MRI versus the CUS, an appropriate statistical methodology is an ROC analysis. This analysis is based on the sensitivity and specificity and compares the diagnostic power over the entire range of the diagnostic variable(s) and thus negates the need to select "cut points". The analysis related to the primary hypothesis will compare the ROC curves for a predictive model based on the MRI data versus a predictive model based on the CUS data. The WPPSI-III < 70 or death after discharge will be the primary outcome variable. The WPPSI-III < 70 among survivors will also be evaluated as an outcome variable.
  - We will conduct the ROC analysis with WPPSI-III<70 (or death after discharge) as the outcome when either MRI or CUS data are in the predictive model and will compare the ROCs for the two models for statistical significance. Since MRI and CUS are done on the same subjects, it will not be necessary to adjust for risk factors in comparing the two tools.
    - In separate analyses, NRN center may be entered as a variable to assess the confounding effects of site. Although CUS and MRI are centrally-read, and significant attempts to ensure reliability and consistency of WPPSI evaluation across sites will be made, unanticipated and unmeasurable differences between sites in quality of neuroimaging or in WPPSI administration *may* confound analyses;
  - We will conduct the ROC analysis with WPPSI-III<70 (or death after discharge) as the outcome when only "traditional variables" (non-neuroimaging variables) are the only variables in the model;
  - We will also do the ROC analysis that compares the contribution of MRI and CUS to the prediction of outcome above and beyond that of the traditional clinical variables.

- Will also do the ROC analysis that compares the incremental value of adding MRI to the prediction of outcome above and beyond that of traditional clinical variables plus CUS
- Logistic regression analysis will be used to compare 6-7 year neurodevelopmental outcomes (or death after discharge) between oxygenation and ventilation SUPPORT randomized groups. These analyses will be adjusted for baseline risk variables.
  - The baseline risk variables pre-specified for adjustment in the main SUPPORT trial are the stratification variables (NRN site and GA group). In comparing 6-7 year outcomes between SUPPORT randomized groups, we plan to adjust only for these variables in our initial approach. However, since the Neuroimaging cohort may not be representative of the originally randomized study cohort, we will investigate differences between the 6-7 year follow-up groups and consider a subsequent level analysis adding other factors if there is an indication of systematic differences.
- Local vs. central neuroimaging secondary analyses: As recommended by the Protocol Review Subcommittee, secondary analyses including evaluation of local MRI reading will be undertaken.
  - Local CUS readings are already collected in the SUPPORT or GDB database; local MRI readings (print-out of final local read with study ID and center written on the document, but patient identifiers removed or blacked out) will be collected.
  - Accuracy of local compared with central neuroimaging interpretation will be performed by sensitivity and specificity analyses (Hintz #2).
  - Additional analyses will compare capability of local MRI read and central MRI read to predict 6-7 year outcomes by ROC analysis.

- "Traditional non-neuroimaging variables": Based on previous investigations assessing the associations of demographic, socioeconomic, perinatal, and neonatal factors with school-age outcomes (Taylor, Doyle #2), we propose the following non-neuroimaging variables will be used in model development; other variables may be considered.
  - Center
  - Gestational age
  - Race
  - Gender
  - Multiple gestation
  - Maternal education level (at baseline)
  - [SUPPORT treatment group]
  - Sepsis or meningitis
  - NEC
  - BPD
  - Postnatal steroids
  - ROP stage III or more severe
  - Length of initial hospital stay (EGA adjusted, i.e., PCA at discharge)

- Any surgery during initial hospitalization

Sample size and power analysis (Primary Hypothesis):

- The sample sizes in the table below are based on formulae for two correlated ROCs (e.g. two ROCs based on the same sample). According to the discussion in the protocol above, we assume that around 350 infants will be available for the 6-7 year IQ evaluation. For a two-tailed test at the 0.05 level of significance and assuming the lowest area under the ROC curve (AUC) for the MRI and the CUS is 75%, the 350 infants would produce the powers in the table below for an array of detectable increases in the AUC and prevalence of outcome.

POWER FOR SELECTED INCREASES FROM 75% IN THE AUC OF THE ROC AND PREVALENCES OF THE PRIMARY OUTCOME:
SAMPLE SIZE = 350

AUC Inc. / Outcome P	5%	6%	7%	8%	9%	10%
20%	31%	43%	55%	67%	77%	86%
25%	37%	50%	64%	76%	85%	92%
30%	42%	56%	70%	81%	90%	95%

Hence, if the prevalence of the primary outcome is as low as 20% a sample size of 350 would pick up an AUC increase of 10% with reasonable power (86%); if the prevalence is 30%, the detectable increase would be 8% (with power 80%).

Budget: The costs of this proposed follow-up study would span over several years. The first enrolled patient will reach the 6th birthday on 05/10/2011, and enrollment is still ongoing. **It is estimated that 6-7 year follow-up windows will extend from May 2011 to early 2016.**

- Tracking: Similar to the Extended Follow-up of the Hypothermia Trial, tracking will be important to ensure the best possible follow-up.
  - Between 18-22 month and 3-4 years: 2 phone contacts with tracking
    - 1 hour/contact at $35/hour
    - Lower estimate: 350ptsx2contactsx1 hour eachx$35= $24,500
    - Upper estimate: 397x2x1x$35=$27,790
  - Between 3-4 years and 6-7 years: 4 contacts (q 6 months)
    - 2 hours/contact at $35/hour
    - Lower estimate: 350x4x2x$35=$98,000
    - Upper estimate:397x4x2x$35=$111,160
- Consents: Consent to contact families for possible 6-7 year follow-up is currently being sought at the 18-22 month visit. Tracking will then commence as noted above. If the proposed 6-7 year follow-up is funded, and depending on the speed

of the process of consents may be obtained at the 18-22 month visit for *some* of the latest enrolling patients; however, it is the most likely scenario that formal signed consent will be obtained at the time of the 6-7 year follow-up visit. It is expected that the consent process will take ~1/2 hour.

- 14 patients were already seen in 18-22 month follow-up prior to Dr. Higgins' announcement to NRN site PI's and Follow-up PI's to request to maintain contact. These patients will require some additional time for tracking/consent. We expect that the consent process will take ~1 hour in this situation
    - Lower estimate:
        - [½ hour x $35/hr x (315-14) patients] + 1 hour x $35 x 14 patients =
            - $5757.50
    - Upper estimate:
        - [½ hour x $35/hr x (357-14) patients] + 1 hour x $35 x 14 patients =
            - $6492.50
- **TOTAL estimate range for tracking and consent: $128,258-145,443**

- Local MRI read: We estimate that relatively little time (~1/2 hour per MRI) will be required to print out/copy final local MRI report, black out patient identifiers, and write in Center number and subject number. These documents will then be sent to RTI.
    - Lower estimate: ½ hour x $35 x 400 MRI's = $7000
    - Upper estimate: ½ hour x $35 x 450 MRI's = $7875
- **TOTAL estimate range for obtaining local MRI read: $7000-7875**

- Training and assuring reliability: The first enrolled SUPPORT Neuroimaging cohort patient will reach the 6th birthday in May 2011. However, given the length of the SUPPORT trial (enrollment expected to be complete early 2009), the final enrolled patients will have 6-7 year follow-up windows that extend from early 2015 to early 2016. Thus, the total cohort follow-up period will span from May 2011 through early 2016. To ensure ongoing training and achieve the best possible reliability for the primary outcome measure (WPPSI-III), we have made the revisions outlined below.
    - Training sessions: We propose adding another WPPSI-III training session for all sites midway through the follow-up (sometime during 2013). As with the Extended Hypothermia Follow-up, these training sessions will also include training in other components of the follow-up exam, including the NEPSY and PEDI. 15 sites are now participating in the SUPPORT Neuroimaging secondary, but the 15th site (Emory) will not have patients reaching the 6th birthday until after 2013. We have also added incrementally to the cost per site in 2013 to adjust for inflation.
        - First training session (prior to May 2011): $3200 x 14 sites = $44,800
        - Second training session (mid-2013): $3400 x 15 sites = $51,000
    - Reliability assessment: In response to Subcommittee comments, we propose ongoing routine exam taping to be sent from participating sites to one of two GOLD STANDARD WPPSI-III psychologists. We propose that,

after training and subsequent certification by one taped exam on a non-study patient, the first 3 exams from each site be taped and sent for review and comment, then every 10th exam. This approach will necessitate a DVD recorder to be purchased by each site. We estimate that 3 hours will be required to review and comment upon each WPPSI-III exam at $60/hour. Gold standard psychologists will assure that turn-around for comments on these exams be rapid so that sites can incorporate feedback in subsequent scheduled patients' visits. Thus, the budget would reflect the following:

- DVD recorders for each site: $350 x 15 sites = $5250
- Review and comment on certification exam =
  - 1 x 15 sites x 3 hours x $60/hr = $2700
- Review 1st 3 exams from each site =
  - 3x15 site x 3 hrs x $60/hr = $8100
- Review of every 10th exam: Dependent on follow-up numbers:
  - If total 357 patients (upper limit) = 30 additional exams x 3 hrs x $60/hr = $5400
  - If total 315 patients (lower limit) = 26 additional exams x 3 hrs x $60/hr = $4680

- **TOTAL estimate – training/consistency assessments: $116,530 - $117,250**

- 6-7 year visit costs:
  - $1000/visit
  - Lower estimate: 315 patients X$1000=$315,000
  - Upper estimate: 357 patientsX$1000=$357,000
- **TOTAL estimate for final visit costs: $315,000-$357,000**

TOTAL BUDGET ESTIMATE: $566,788 - $627,568

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Patient Tracking Tool

6-7 year SUPPORT Follow-up

Red items: RTI provides

Name MR # Study #

DOB _____ 3rd birthday _____ 6th birthday _____

Contact Name:	Relationship:
Address:	
Telephone #'s:	
Email(s):	

Contact Name:	Relationship:
Address:	
Telephone #'s:	
Email(s):	

Contact Name:	Relationship:
Address:	
Telephone #'s:	
Email(s):	

Contact Name:	Relationship:
Address:	
Telephone #'s:	
Email(s):	

Contact Name:	Relationship:
Address:	
Telephone #'s:	
Email(s):	

6-7 Year SUPPORT follow-up SITE TRACKING LIST **Red/bold: RTI data**; italic:site data

Patient Name	*MR #*	**Study #**	**DOB**	**18 months**	**22.5 months**	*month status*	**3 years**	**4 years**	*3-4 year status*	**6 years**	**7 years**	*6-7 year status*
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	

From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OUTCOMES
Date: Friday, October 24, 2008 10:05:24 AM

Hey Rose,

Patricia forwarded this to me. I wanted to let you know that I took over Sharon Wright's position, so you can e-mail any information to me at Margaret.Poundstone@uth.tmc.edu instead of Sharon. Thanks so much!

Margaret Layne Poundstone, RN, BSN
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wed 10/22/2008 3:24 PM
To: Kennedy, Kathleen A; Tyson, Jon E; Mcdavid, Georgia E; Evans, Patricia W; Wright, Sharon
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
CENTER	NETWORK	BPD_message
18	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18	(b) (6)	FU window has closed but NF09a has not been completed
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, October 24, 2008 9:11:51 AM

Did you get a response on this?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:35 PM
To: Wilson, Leslie Dawn; Poindexter, Brenda B
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT

So they did not consent for breathing outcomes, correct? If so, those forms should be deleted. Was the death an in-hospital or post-discharge death? If in-hospital, it should get reflected on GDB. If post-discharge, we will need the NF-12 3.b filled out.

Thanks
Rose

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Wednesday, October 22, 2008 4:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Das, Abhik; Marie Gantz
Subject: RE: SUPPORT

Hi. This infant passed away(b) (6) For Breathing Outcomes, there was a SUPP01, 02, and 03 completed, stating that the interviews were not done because of the death. I had requested that even this be removed from the network database as there was no consent obtained for pt to ever be in this sub-study.

Thank you-leslie

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
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317.312.1121 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:14 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: RE: SUPPORT follow up
Date: Thursday, October 23, 2008 5:30:46 PM
Attachments: Follow6_7yearNeuroSUPPORT033008.doc

Hi Rose

How about this - Can't we send them the "final" protocol as approved by the Steering Committee (attached)? This will at least detail the timing of visit (which will not change), the hypotheses for the study (which will not change) and the *general* tests and instruments for assessment that will occur at 6-7 year visit. Do you think that would be acceptable? Also in the protocol is the *reasoning for need to begin tracking* - that might help.

Susan

Delivered-To: srhintz@stanford.edu
Subject: RE: SUPPORT follow up
Date: Thu, 23 Oct 2008 16:22:48 -0500
Thread-Topic: SUPPORT follow up
Thread-Index:
AchlFq1rjGyJvaikTViayfCv7NJDrwAAkQhgNAt1n6AAAL18MAABECngAAFpAsAAAFDr8
A==
From: "Johnson, Karen" <karen-johnson@uiowa.edu>
To: "Bell, Edward" <edward-bell@uiowa.edu>,
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>,
"Susan Hintz" <srhintz@stanford.edu>,
"Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>
Cc: "Zaterka-Baxter, Kristin" <kzaterka@rti.org>
X-OriginalArrivalTime: 23 Oct 2008 21:22:48.0849 (UTC) FILETIME=
[7FBF1010:01C93555]

I just talked to them. As I suspected, she said the board won't approve us keeping in contact with them without giving them some justification/plan as to why we want to see them then and what we will do with them at the 6-7 year visit. It doesn't have to be exactly what we will do and we can qualify it with a statement that this is subject to change due to the fact that the protocol is not fully developed yet and that we are just asking to be able to keep track of them. She said as much information as we can give them about the plan for the 6-7 year follow up protocol is best.

Karen

From: Bell, Edward
Sent: Thursday, October 23, 2008 4:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Susan Hintz; Archer, Stephanie (NIH/NICHD) [E]
Cc: Johnson, Karen; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

I think we can submit it as a protocol modification, but Karen thinks they may ask for more information about how and when we will recontact parents. (Karen, feel free to chime in.)

Ed

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 3:30 PM
To: Bell, Edward; Susan Hintz; Archer, Stephanie (NIH/NICHD) [E]
Cc: Johnson, Karen; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

Ed

We have some tracking tools - can you tell me if your IRB requires the final protocol or can you "add on" a clause to re-contact parents either in the SUPPORT or FU consents?

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Thursday, October 23, 2008 4:02 PM
To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Cc: Johnson, Karen
Subject: FW: SUPPORT follow up

Susan, Rose, or Stephanie,

Can you help us with what to provide the IRB about the plan to contact families for the 6-7-yr follow-up.

Thanks,

Ed

From: Johnson, Karen
Sent: Thursday, October 23, 2008 2:39 PM
To: Bell, Edward
Subject: RE: SUPPORT follow up

Ed,

I am going to submit this to the IRB along with an increase in the compensation for follow-up and the latest DSMC report. Is there a more official notice about the request to re-contact the family for the 6-7 year FU study? I anticipate our IRB having an issue with asking parents if we can continue to contact them without a solid plan in place.

KJ

From: Bell, Edward
Sent: Friday, February 01, 2008 3:25 PM
To: Johnson, Karen
Subject: FW: SUPPORT follow up

Importance: High

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 01, 2008 3:09 PM
To: rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: nfiner@ucsd.edu; Susan Hintz; Archer, Stephanie (NIH/NICHD) [E]; Newman, Jamie; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: SUPPORT follow up
Importance: High

Hi,

The protocol review committee reviewed the SUPPORT 6-7 year FU study submitted by Susan Hintz today. The subcommittee is requesting revisions and a re-review of the protocol prior to forwarding to the steering committee. There is significant enthusiasm for this study. In the meantime, the committee is asking that sites seeing patients in follow up who have had the neuroimaging studies done as a secondary to the SUPPORT Trial to **request permission to re-contact the family** in the event that the 6-7 year FU study goes forward.

Let me know if there are any questions.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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Extended follow-up at 6-7 years of age of patients enrolled in the Neuroimaging and Neurodevelopmental Outcome Secondary to SUPPORT

Subcommittee:

Susan Hintz, M.D., M.S. Epi.
Betty Vohr, M.D.
Maureen Hack, M.D.
Neil Finer, M.D.
W. Kenneth Poole, Ph. D.
Jane Hammond, Ph.D.
Abhik Das, Ph.D.
Seetha Shankaran, M.D.
M. Bethany Ball
Rosemary Higgins, M.D.

I) ABSTRACT:

The NICHD NRN SUPPORT Neuroimaging cohort will be the largest cohort of extremely preterm infants with brain magnetic resonance imaging (MRI). Children born extremely prematurely continue to have significant neurodevelopmental challenges in later childhood; many subtle yet significant cognitive and performance problems cannot be delineated until 5-8 years and beyond. Early and accurate prediction of neurodevelopmental outcome would be invaluable, but cranial ultrasound (CUS) and other early variables do not reliably predict outcomes. White matter (WM) injury has been strongly implicated in both neuromotor and cognitive impairment, and a developmental neuroanatomical link between WM injury and gray matter disruption appears to exist. MRI is better than CUS in identifying subtle and diffuse WM injury, as well as cerebellar, and gray matter abnormalities. Small and larger studies to date, including the 2-year New Zealand premie MRI cohort results, have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities. But a significant association of MRI abnormalities with cognitive impairment at 18-24 months has not yet been reported. However, subtle neonatal MRI abnormalities may predict cognitive problems in early school age that cannot be delineated in very early childhood. Death after discharge is a competing outcome for outcome at 6-7 years. **Therefore, we propose a 6-7 year neurodevelopmental follow-up of the SUPPORT Neuroimaging cohort to test the hypothesis that neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment and disability at 6-7 years. We will also assess whether injury severity on neonatal MRI will be associated with longitudinal cognitive and disability level changes. In addition, we will examine cognitive impairment and disability between ventilatory or oxygenation saturation SUPPORT intervention groups.** The SUPPORT Neuroimaging cohort is valuable and unique among other worldwide premie MRI cohorts; by undertaking 6-7 year follow-up, the NICHD NRN is in an outstanding position to substantially contribute to the understanding of the later outcomes of extremely preterm infants and their prediction.

Hypotheses: Among <28-week EGA children enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary, surviving to hospital discharge:

PRIMARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or cognitive impairment (WPPSI-III IQ<70) at 6-7 years

SECONDARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment (WPPSI-III IQ<70) at 6-7 years
- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or disability at 6-7 years
- Neonatal brain MRI will be superior to neonatal CUS in predicting disability at 6-7 years
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the frequency of death after discharge or cognitive impairment, disability,

or cerebral palsy between ventilatory or oxygenation saturation SUPPORT intervention groups in this sub-cohort.

- Neonatal brain MRI will be superior to neonatal CUS in predicting death after discharge or CP at 6-7 years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting CP at 6-7 years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting mild-moderate cognitive impairment (WPPSI-III 1-2 SD below population mean) at 6-7 years
- Local readings of neonatal MRI will be less predictive of 6-7 year outcomes than central reading
- Compared to central reading, local readings of both neonatal CUS and MRI will moderately to highly accurate for overall abnormal or severely abnormal findings, but poorly accurate for subtle findings.
- Injury severity and pattern on neonatal MRI will be associated with longitudinal cognitive and disability level changes
- Brain injury pattern and topography on neonatal MRI will be associated with anatomic and functional type of CP

Specific Aims:

- To assess cognitive, neuromotor, functional and behavioral outcomes of the SUPPORT Neuroimaging cohort at 6-7 years of age
- To examine the independent associations of neonatal neuroimaging findings with neurodevelopmental outcomes
    - Assess the absolute and relative value of early and late neonatal CUS and neonatal MRI, alone and in combination with other risk factors, to predict normal and impaired outcomes
- To examine longitudinal changes in cognitive and overall impairment level from 18-22 month to 6-7 year exams, and assess relationship of neonatal neuroimaging abnormalities and other variables.
- To compare 6-7 year neurodevelopmental outcomes of ventilation and oxygenation SUPPORT randomized groups in this sub-cohort.

II) BACKGROUND AND SIGNIFICANCE:

Long-term neurodevelopmental outcomes of extremely preterm infants:

Despite advances in perinatal and neonatal management and improvement in survival, short-term neurodevelopmental outcomes of extremely preterm and extremely low birth weight (ELBW) infants appear to remain guarded (Vohr, Hintz, Costeloe). This reported high frequency of disability in very early childhood (18-24 months) makes longer-term neurodevelopmental outcome studies crucial. Evaluation at a later age allows identification and delineation of a broader range of problems, including cognitive delay, more subtle motor disabilities, and behavioral problems to be determined. It also allows for assessment of the strength of perinatal and neonatal variables as potential predictors of long-term outcome, and for longitudinal analysis to determine the predictive value of early disability.

Later childhood follow-up studies have demonstrated that significant neurodevelopmental and cognitive impairment continue. In the 206 ELBW infants

followed at 5 years in the Finnish National Cohort (Mikkola), 20% had major disabilities, and 19% of those <27 weeks were diagnosed with cerebral palsy (CP). The EPICure Study Group (Marlow) reported on 241 <26 week survivors at 6 years; severe overall cognitive delay was present in 21% compared with test norms (41% compared with term controls), and disabling CP was diagnosed in 13%. In a study of 219 ELBW infants 8 years (Hack), Hack, et. al. reported CP in 14%, severe cognitive impairment in 15%, moderate-severe cognitive impairment in 38%, and significant motor skills problems in 27%. Families reported substantial functional limitations, including emotional delay, trouble understanding or communicating, and need for medication or equipment; needs for special services were significantly greater than for the normal birth weight (NBW) control group. Impairment in academic (32%) and adaptive skills (48%) have also been reported among ELBW children, and are significantly more frequent than in NBW controls (Taylor). In an ELBW or <28 week EGA cohort at 8 years (n=275), Anderson, et. al. reported significant impairment across all tested cognitive and educational abilities compared with NBW controls (Anderson).

Summary: Children born extremely preterm or ELBW continue to have substantial motor and cognitive disabilities in childhood, as well as more subtle functional and adaptive impairments. Delineation of some of these problems may not even be reasonably undertaken until 5-8 years of age. The true impact of these impairments may not be felt until later school age (Saigal).

Predicting neurodevelopmental outcome: Neonatal CUS and other variables:

CUS and short-term (18-24 months)

The association of a combination of severe neonatal CUS abnormalities and adverse short-term neurodevelopmental outcome has been reported in numerous studies (Vohr, Hack#2). But, even in the most detailed CUS studies, the strength of this association appears to be consistent primarily for combined endpoints, or for CP or motor disability, but not for pure cognitive delay (deVries, Hack #2, Wood). In addition, severe CUS abnormalities are not uniformly predictive of adverse short-term outcome and normal CUS do not predict normal outcome in this high-risk population (deVries, Hack#2, Laptook, Ancel, Pinto-Martin). In fact, in a predictive modeling analysis, Ambalavanan found that severe grade of IVH explained only 8% of the variance in low MDI and 5% of the variance for major handicap at 18-22 months (Ambalavanan).

CUS and long-term outcome (5-8 years)

Reported associations of neonatal CUS findings and long-term outcomes are inconsistent. Sherlock, et. al. (Sherlock) reported that neurodevelopmental impairment at 8 years varied little with increasing severity of IVH; a trend for worse cognitive and neurosensory outcome with higher grade IVH explained solely by the outcomes of the small number of patients with parenchymal hemorrhage. Similarly, 6-year results of the Neonatal Brain Hemorrhage Study (NBHS) showed that 88% of LBW patients with germinal matrix or IVH had normal cognitive outcomes (Whitaker).

Nevertheless, several analyses have reported abnormal neonatal CUS to be "significantly associated with" adverse long-term neurodevelopmental outcomes in ELBW cohorts. For instance, Mikkola found an association of abnormal CUS with CP and IQ at 5 years (Mikkola), and Taylor found an association of abnormal CUS with

executive function and memory on the NEPSY (Taylor). However, the definition of CUS "abnormality" varies among studies, with some analyses including markers of white matter injury (PVL or ventricular enlargement (VE)) and others limiting only to IVH. In addition, a finding of association does not specifically address the independent *predictive* power of neonatal CUS, particularly with respect to cognitive outcome in later childhood. In fact, Hack, et. al. demonstrated that only 36% of those with a Mental Processing Composite (MPC) of <85 at 8 years had had an abnormal CUS, and only 45% of those with MPC<70 (Hack #3). In the 6-year follow-up of the NBHS cohort, only 12% of those with GM/IVH had borderline IQ or mental retardation (Whitaker). In that study, PVL/VE was separately assessed; this revealed a stronger 56.5% of those with PVL/VE had borderline IQ or mental retardation. This may be a clinical insight to the importance of white matter (WM) injury for longer-term adverse outcomes *including cognitive outcomes*. Nevertheless, more that 40% of patients with PVL/VE had normal intelligence at 6 years - a finding, which, in turn, may serve to underscore the inability of routine CUS to see anything more subtle than the most definitive WM injury.

Other potential predictors of long-term neurodevelopmental outcome:

Investigators have attempted to determine other, more reliable predictors of longer-term outcomes of preterm infants. Doyle reported on prediction of survival free of major disability at 5 years among the surviving VICS cohort on the basis of the number of "adverse neonatal variables" (Doyle #2). Although observed and predicted values were similar, the outcome was not specifically focused (i.e., combined neurologic/neurosensory/cognitive endpoint), the observed 95% CI range was broad for 2 and 3 variable groups, and the patient numbers were quite small. Others have assessed the predictive value of *earlier neurodevelopmental findings*. Marlow found that only severe disability at 30 months was highly predictive of 6-year outcome; 38% of children defined as mild or moderately disabled and 24% with "no disabilities" had moderate or severe disabilities at 6 years. Hack (#3) found the positive predictive value of MDI<70 at 20 months for MPC<70 at 8 years to be extremely poor (PPV=0.37). However, some intriguing links of longitudinal decline in cognitive ability with brain injury have been reported. In follow-up to the I-IVHP trial, Ment found that cognitive scores declined from 36 to 96 months only in the subset of patients with early IVH coupled with PVL or VE (Ment). Also from the I-IVHP trial, the presence of spastic cerebral palsy at 3 years was more strongly predictive of IQ<70 at 8 years than was cognitive testing at 3 years (Pleacher). These findings are not surprising, in part due to the potential mechanism linking white matter injury with reduced connectivity, gray matter loss, and cognitive delay.

Summary: Aggregate abnormal findings on neonatal CUS do not reliably predict either short- or long-term neurodevelopmental outcomes, although markers of WM injury appear to be stronger links. Early cognitive measures also do not predict later cognitive outcome well in most circumstances. These findings emphasize the deficits of routine CUS to detect subtle injury, and also underscore the poor predictive validity of early cognitive measures for later cognitive outcomes (Aylward).

MRI: Delineation of injury and predicting outcomes

Imaging injury:

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Studies comparing the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period have concluded that MRI detects white matter injury better than CUS (Maaloof, Childs), and provides additional information on brain development not noted by cranial US. Studies have also demonstrated that subtle and diffuse WM injury, not detectable by CUS, may be common among preterm infants at term (Counsell).

White matter injury and cognitive outcome:

Cognitive delay is a significant and difficult to predict component of the range of impairments. Recent studies have demonstrated that white matter injury in the preterm infant is associated with both reduced cortical gray matter volume, and with reduced deep gray matter volume by MRI at term equivalent age (Inder, Boardman). There are several potential mechanistic pathways, including via direct axonal or subplate neuron injury that may explain this finding. The common endpoint is reduced connectivity, limited neuronal differentiation, and poor cognitive outcome. In fact, recent research using MRI tractography in a series of former preterm infants at approximately 2 years of age has provided evidence for this theory of reduced cortical and thalamic connections after WM injury (#2 Counsell).

MRI in preterm infants and early neurodevelopmental outcome

After early studies suggesting that MRI at near term was a more powerful predictive tool than CUS for short-term neurodevelopmental outcome (Valkama, Roelents-van-Rijn, Mirmiran), larger MRI studies were undertaken. Many have been single-center efforts, focused chiefly on the association of early neurodevelopmental outcomes with MRI findings in preterm infants at term and earlier, and without extensive comparison of the predictive validity of MRI and CUS. Among these, Miller, et. al. (UCSF, <34 weeks EGA, 86 survivors) and Dyet, et. al. (Hammersmith, <30 weeks EGA, 119 survivors) described MRI findings from birth through near-term and found that WM injury, particularly diffuse injury, was common and was associated with adverse neurodevelopmental outcomes. Cerebellar injury, not easily seen with routine CUS, was also a prognostic indicator of poor outcome. Of importance, although MRI data were meticulously obtained, only 66% of the group had complete follow-up data.

However, other groups have preterm/MRI cohorts, with research aims that include comparison of predictive capabilities of MRI and CUS.

- The recently reported 2-year neurodevelopmental outcomes of the New Zealand (NZ) cohort (Woodward) (<30 weeks EGA, 167 survivors) revealed that 1) presence of moderate-severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) although increasing severity of WM injury was associated with worse Bayley MDI scores, an independent association of moderate-severe WM injury with severe cognitive delay was not reached. Although sensitivity of moderate-severe WM to predict CP (65%), neurosensory impairment (82%) and severe cognitive delay (41%) was improved over abnormalities on CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n=29) or severe (n=6) WM injury was small, and approximately half of those did not have neurodevelopmental impairment.

- The 2-years results of the Australian cohort (<1250 g or <30 weeks EGA, n=221) were reported at the 2007 PAS (Hunt). "Major" white matter injury was found to be a more significant independent risk factor than PVL for CP, and was an independent risk factor for neurosensory disability where PVL was not. IVH grade 4 was not found to be a significant risk factor for either outcome.
- **SUPPORT Neuroimaging cohort:** Continuing enrollment; first enrolled birth date 5/10/05. Follow-up at 18-22 months ongoing.

SUPPORT Neuroimaging cohort: Unique and valuable

The SUPPORT Neuroimaging cohort, estimated to include 400-450 survivors with complete CUS and MRI data by the time SUPPORT enrollment closes, will be the largest preterm/MRI/follow-up cohort worldwide. This cohort is also a higher-risk group than other cohorts, and thus innately targets the most important outcomes group. Follow-up at 18-22 months is in progress, with the first enrolled SUPPORT Neuroimaging patient follow-up window 2/6/07-6/21/07. The SUPPORT Neuroimaging cohort is inherently exceptional and unique in that it was developed within a randomized controlled trial. Thus, the management profile of a crucial neonatal care component has been more carefully controlled and monitored than would otherwise be the case. This also allows for secondary analyses of the association of respiratory management strategies with subtle MRI findings and outcome. The SUPPORT Neuroimaging cohort also has a number of advantages over other preterm/MRI cohorts:

1) New Zealand (NZ) cohort:
    a. Setting: SUPPORT: Embedded in a randomized controlled trial within a multicenter network with focused neurodevelopmental follow-up priorities; NZ: two centers one in New Zealand another in Melbourne, Australia, with a primary focus on MRI imaging
    b. EGA/risk profile:
        i. SUPPORT: <28 weeks EGA; NZ cohort: <30 weeks. Only 87/167 of the NZ cohort was <1000 g BW, and 95/167 were <28 weeks.
    c. Cohort size: SUPPORT: estimated 400-450 survivors; NZ: 167 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. SUPPORT: Two specifically-timed and required CUS, including near-term; NZ: within 2 days, 5-7 days, 4-6 weeks; if "abnormality" detected, more frequent performed.
        ii. SUPPORT: central reader, detailed central reader data instrument; NZ: No central reader. "Worst" CUS findings recorded only with respect to PVL/echolucency, grade 3 or 4 IVH
    e. Timing/interpretation of MRI:
        i. BOTH: Near-term
        ii. BOTH: Central reader
        iii. SUPPORT: detailed MRI central reader form; NZ: central reader data collection instrument not known, but MRI abnormality categories broad.
    f. Non-imaging data collection:
        i. SUPPORT: extensive, including detailed respiratory data; NZ: less detailed

2) Australia cohort:
    a. Setting: Single center in Melbourne, Australia
    b. EGA/risk profile:
        i. <30 weeks, <1250 g.
    c. Cohort size: 221 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. Not required, retrospectively gather information (communication, Rod Hunt).
        ii. "Worst" CUS findings gathered - PVL, grade 4 IVH
    e. Timing/interpretation of MRI:
        i. Near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
3) Hammersmith cohort:
    a. Setting: Single center
    b. EGA/risk profile:
        i. <30 weeks.
    c. Cohort size: 119 survivors at 2 years. **Note: complete follow-up data were available for only 66% of the group**
    d. Timing/interpretation of CUS:
        i. CUS not focus – studies thus far report MRI
    e. Timing/interpretation of MRI:
        i. MRI serial – from birth to near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
4) UCSF:
    a. Small, single center
    b. <34 weeks
    c. 86 survivors at 2 years
    d. CUS not focus – MRI's serial from birth to near-term
    e. Non-imaging data routine

Summary: MRI is better than CUS in identifying subtle and diffuse white matter injury, which is relatively common among preterm infants at term, as well as cerebellar, and gray matter abnormalities. Earlier small studies suggested that MRI better predicts adverse neuromotor outcome than CUS. Two-year results of the NZ cohort have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities, but not with adverse cognitive outcome. The extent to which these findings will be enhanced and clarified, and how or when MRI should be applied in routine clinical practice, awaits the 18-22 month results of the larger, higher-risk SUPPORT Neuroimaging cohort. However, a biologic mechanism for the link between WM injury and cognitive impairment exists. Early cognitive findings are poor predictors of later challenges, and subtle neonatal MRI abnormalities may predict subtle problems in early school-age that cannot be delineated at 18-22 months.

Later outcomes: Need for SUPPORT Neuroimaging extended follow-up

Evidence for altered brain development: corroboration of need for long-term follow-up

Short-term neurodevelopmental outcomes are only a tiny window into the future of a former preterm child. Difficulties in cognition, performance, verbal/language skills, attention and behavior may not be delineated until later ages. There are also data to support the concept that even minor, undiagnosed brain injury sustained preterm infant is associated with disordered brain development. The degree of white matter injury purported to be associated with reduced connectivity and subsequent gray matter reduction may be subtle, and its effects dependent on other variables (Inder, Boardman). Rademaker, et. al. found that even minor differences in lesion severity on MRI performed at 8 years of age in <32 week EGA appeared more accurate in prediction of IQ and total impairment score than neonatal CUS (Rademaker). These findings may suggest that subtle injury could have been seen on *neonatal* MRI, which in turn, could have aided in prediction. In a DTI and volumetric MRI study, Yung demonstrated that *neurologically normal* LBW preterm infants at 8-12 years had significantly reduced WM volumes than term controls, and that this was significantly related to reduced IQ (Yung). This finding again suggests that early WM injury leading to reduced volume may have been identifiable on neonatal MRI. Kesler, et. al. described high-resolution MRI results from 73 preterm and 33 term infants at 7-11 years of age; preterm infants had disorganized cortical development, potentially involving disrupted neural migration (Kesler).

Importance of SUPPORT Neuroimaging secondary long-term follow-up

The importance of long-term follow-up for any preterm cohort with neonatal MRI's is clear.

- Our current ability to predict later childhood outcomes from perinatal and neonatal variables is limited. The prognostic validity of neonatal CUS findings is limited. Even early childhood neurodevelopmental outcome, apart from severe impairment, do not accurately predict later childhood neurocognitive outcome. MRI holds promise as a better predictive modality, but neonatal MRI has not been evaluated with respect to truly long-term outcomes.
- Performance skills are different at 18-22 months than 6-7 years; assessments at the later age may uncover subtle, yet significant problems, which may be associated brain injury seen by neonatal MRI.
    - Such assessments may reveal attention/behavior problems, language and verbal delays, more detailed picture of cognitive/academic impairment.

But the **SUPPORT Neuroimaging cohort is unique among other cohorts, and is in an outstanding position to substantially contribute to the understanding of neonatal imaging and prediction of long-term neurodevelopmental outcomes**:

- SUPPORT Neuroimaging secondary designed with MRI/CUS predictive comparison in mind, thus careful attention to specifically-timed CUS, detailed central reading of all study neuroimaging
- 18-22 month follow-up is already part of this secondary study

    - Thus, crucial opportunity to evaluate longitudinal changes, and importantly, brain injury patterns or other variables associated with changes in cognitive or functional outcomes
- Prospectively enrolled secondary cohort, embedded within SUPPORT RCT; more consistent management of respiratory approach, comprehensive data collection
    - Opportunity for secondary analyses of randomized ventilation/oxygenation arms of Neuroimaging cohort outcomes at 6-7 years
- Study within the NICHD NRN; neurodevelopmental follow-up is already a focused objective, and follow-up rates have been outstanding for previous trials (Shankaran)
- SUPPORT cohort will be the largest and highest-risk cohort of premature infants with CUS and MRI. Much has already been invested in this valuable cohort.

In addition, it is important to recognize that other preterm/MRI cohorts, notably the NZ cohort, already have protocols in place for long-term follow-up. The NZ cohort 4-5 year follow-up is underway (communication, TE Inder).

Why we can't wait to commit to 6-7 year follow-up:

Finally, it may appear premature to plan for 6-7 year follow-up of this sub-cohort within a RCT that is still enrolling. It may seem reasonable to wait to assess 18-22 month outcome results, and commit to follow-up only after that point. But that approach will not be possible. The birth date of the first SUPPORT Neuroimaging subject was 5/10/2005. If current enrollment rate continues, SUPPORT enrollment will not likely be completed until early 2009. Thus, in the best possible scenario, the final SUPPORT Neuroimaging subject would have an 18-22 month follow-up window *opening* in early 2011, while the first SUPPORT Neuroimaging subject will reach the 6th birthday on 5/10/2011. **Therefore, analysis would not be complete for 18-22 month outcomes soon enough to allow for 6-7 year follow-up tracking, planning and preparation.**

III) STUDY DESIGN:

Objective: This is a proposed prospective follow-up study of the 6-7 year neurodevelopmental outcomes of the SUPPORT Neuroimaging Secondary cohort. We will evaluate and compare the capabilities of *neonatal neuroimaging* - CUS and near-term MRI – to predict cognitive impairment, disability, and neuromotor impairment at 6-7 years. We will evaluate longitudinal changes in neurodevelopmental outcome, and assess associated neuroimaging findings and other variables. We will also determine if ventilatory or oxygenation saturation SUPPORT interventions are associated with differences in 6-7 year neurodevelopmental outcomes.

Outcomes:

- Primary:
    - IQ by WPPSI-III<70
        - Because death after discharge is a competing outcome, the primary outcome will be WPPSI-III<70 *or* death after discharge
- Secondary:

- IQ score (continuous) by WPPSI-III
- Disability
  - Severe: Any of: WPPSI IQ >3 SD below mean, severely impaired neuromotor/functional outcome (non-ambulatory, GMFCS level 4-5), profound hearing loss or blindness (not functionally correctable),
  - Moderate: Any of: WPPSI IQ 2-3 SD below mean, moderately impaired neuromotor/functional outcome
  - Mild: Any of: WPPSI IQ 1-2 SD below mean, mildly impaired neuromotor/functional outcome (abnormal neurologic exam, but walking independently, GMFCS level 1-2)
- Cerebral palsy
  - Classified anatomically and functionally according to Definition and Classification of Cerebral Palsy, April 2006 guidelines
- Mild cognitive impairment (WPPSI IQ 1-2 SD below mean) and severe cognitive impairment (WPPSI IQ>3 SD below mean)
- Behavioral and attention deficits
- Chronic conditions and functional limitations

Study population:

- The study population (SUPPORT Neuroimaging cohort) will be comprised of the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary enrollees who survived to discharge. **By the time SUPPORT enrollment in completed, it is estimated that 400-450 infants will be in the SUPPORT Neuroimaging cohort.**
- As described in the SUPPORT Neuroimaging and Neurodevelopmental outcome secondary, these patients will have had two CUS (early: 4-14 days of age; late: 35-42 weeks and within 5 days of MRI) and a brain MRI at 35-42 weeks.
  - The CUS with the most severe abnormalities (the "worst" CUS) will be used in comparative analyses
- Estimated cohort size at neurodevelopmental follow-up
  - Follow-up at 18-22 months (ongoing)
    - Estimate 2% death after discharge, 10% loss to F-U: **cohort=350-397 pts**
  - Follow-up at 6-7 years
    - Estimate additional 10% loss to F-U: **cohort = 315-357 pts**

Design:

- This proposed protocol concept is a long-term cognitive, neurologic, and functional follow-up of the SUPPORT Neuroimaging Cohort. **No further neuroimaging is being proposed**.
- Visit at 6-7 years:
  - Neurologic exam and Gross Motor Function exam
    - Diagnosis of CP, type (anatomic description), and severity (Rosenbaum);
    - Gross Motor Function Classification level
    - Fine motor assessment
  - Weschsler Preschool and Primary Scale of Intelligence- III

- NEPSY
- ** Pediatric Evaluation of Disability Inventory (PEDI)**
  - For children unable to be tested by the WPPSI and NEPSY due to severe neurodevelopmental impairment
- Medical history
- Socioeconomic status (SES)
  - SES data will be assessed by a questionnaire that parallels that of the 18-22 month visit and baseline.
- Questionnaire for Identifying Children with Chronic Conditions (QUICCC)
- Attention/behavior instruments:
  - Child Behavior Checklist (CBCL)
  - Conners' Rating Scale
- Impact on Family questionnaire

Statistical considerations:
Analyses:

- Since we are concerned with the relative diagnostic power of the MRI versus the CUS, an appropriate statistical methodology is an ROC analysis. This analysis is based on the sensitivity and specificity and compares the diagnostic power over the entire range of the diagnostic variable(s) and thus negates the need to select "cut points". The analysis related to the primary hypothesis will compare the ROC curves for a predictive model based on the MRI data versus a predictive model based on the CUS data. The WPPSI-III < 70 or death after discharge will be the primary outcome variable. The WPPSI-III < 70 among survivors will also be evaluated as an outcome variable.
  - We will conduct the ROC analysis with WPPSI-III<70 (or death after discharge) as the outcome when either MRI or CUS data are in the predictive model and will compare the ROCs for the two models for statistical significance. Since MRI and CUS are done on the same subjects, it will not be necessary to adjust for risk factors in comparing the two tools.
    - In separate analyses, NRN center may be entered as a variable to assess the confounding effects of site. Although CUS and MRI are centrally-read, and significant attempts to ensure reliability and consistency of WPPSI evaluation across sites will be made, unanticipated and unmeasurable differences between sites in quality of neuroimaging or in WPPSI administration *may* confound analyses;
  - We will conduct the ROC analysis with WPPSI-III<70 (or death after discharge) as the outcome when only "traditional variables" (non-neuroimaging variables) are the only variables in the model;
  - We will also do the ROC analysis that compares the contribution of MRI and CUS to the prediction of outcome above and beyond that of the traditional clinical variables.

- Will also do the ROC analysis that compares the incremental value of adding MRI to the prediction of outcome above and beyond that of traditional clinical variables plus CUS
- Logistic regression analysis will be used to compare 6-7 year neurodevelopmental outcomes (or death after discharge) between oxygenation and ventilation SUPPORT randomized groups. These analyses will be adjusted for baseline risk variables.
  - The baseline risk variables pre-specified for adjustment in the main SUPPORT trial are the stratification variables (NRN site and GA group). In comparing 6-7 year outcomes between SUPPORT randomized groups, we plan to adjust only for these variables in our initial approach. However, since the Neuroimaging cohort may not be representative of the originally randomized study cohort, we will investigate differences between the 6-7 year follow-up groups and consider a subsequent level analysis adding other factors if there is an indication of systematic differences.
- Local vs. central neuroimaging secondary analyses: As recommended by the Protocol Review Subcommittee, secondary analyses including evaluation of local MRI reading will be undertaken.
  - Local CUS readings are already collected in the SUPPORT or GDB database; local MRI readings (print-out of final local read with study ID and center written on the document, but patient identifiers removed or blacked out) will be collected.
  - Accuracy of local compared with central neuroimaging interpretation will be performed by sensitivity and specificity analyses (Hintz #2).
  - Additional analyses will compare capability of local MRI read and central MRI read to predict 6-7 year outcomes by ROC analysis.

- "Traditional non-neuroimaging variables": Based on previous investigations assessing the associations of demographic, socioeconomic, perinatal, and neonatal factors with school-age outcomes (Taylor, Doyle #2), we propose the following non-neuroimaging variables will be used in model development; other variables may be considered.
  - Center
  - Gestational age
  - Race
  - Gender
  - Multiple gestation
  - Maternal education level (at baseline)
  - [SUPPORT treatment group]
  - Sepsis or meningitis
  - NEC
  - BPD
  - Postnatal steroids
  - ROP stage III or more severe
  - Length of initial hospital stay (EGA adjusted, i.e., PCA at discharge)

- Any surgery during initial hospitalization

Sample size and power analysis (Primary Hypothesis):

- The sample sizes in the table below are based on formulae for two correlated ROCs (e.g. two ROCs based on the same sample). According to the discussion in the protocol above, we assume that around 350 infants will be available for the 6-7 year IQ evaluation. For a two-tailed test at the 0.05 level of significance and assuming the lowest area under the ROC curve (AUC) for the MRI and the CUS is 75%, the 350 infants would produce the powers in the table below for an array of detectable increases in the AUC and prevalence of outcome.

POWER FOR SELECTED INCREASES FROM 75% IN THE AUC OF THE ROC AND PREVALENCES OF THE PRIMARY OUTCOME:
SAMPLE SIZE = 350

AUC Inc. / Outcome P	5%	6%	7%	8%	9%	10%
20%	31%	43%	55%	67%	77%	86%
25%	37%	50%	64%	76%	85%	92%
30%	42%	56%	70%	81%	90%	95%

Hence, if the prevalence of the primary outcome is as low as 20% a sample size of 350 would pick up an AUC increase of 10% with reasonable power (86%); if the prevalence is 30%, the detectable increase would be 8% (with power 80%).

Budget: The costs of this proposed follow-up study would span over several years. The first enrolled patient will reach the 6th birthday on 05/10/2011, and enrollment is still ongoing. **It is estimated that 6-7 year follow-up windows will extend from May 2011 to early 2016.**

- Tracking: Similar to the Extended Follow-up of the Hypothermia Trial, tracking will be important to ensure the best possible follow-up.
  - Between 18-22 month and 3-4 years: 2 phone contacts with tracking
    - 1 hour/contact at $35/hour
    - Lower estimate: 350ptsx2contactsx1 hour eachx$35= $24,500
    - Upper estimate: 397x2x1x$35=$27,790
  - Between 3-4 years and 6-7 years: 4 contacts (q 6 months)
    - 2 hours/contact at $35/hour
    - Lower estimate: 350x4x2x$35=$98,000
    - Upper estimate:397x4x2x$35=$111,160
- Consents: Consent to contact families for possible 6-7 year follow-up is currently being sought at the 18-22 month visit. Tracking will then commence as noted above. If the proposed 6-7 year follow-up is funded, and depending on the speed

of the process of consents may be obtained at the 18-22 month visit for *some* of the latest enrolling patients; however, it is the most likely scenario that formal signed consent will be obtained at the time of the 6-7 year follow-up visit. It is expected that the consent process will take ~1/2 hour.

- 14 patients were already seen in 18-22 month follow-up prior to Dr. Higgins' announcement to NRN site PI's and Follow-up PI's to request to maintain contact. These patients will require some additional time for tracking/consent. We expect that the consent process will take ~1 hour in this situation
    - Lower estimate:
        - [½ hour x $35/hr x (315-14) patients] + 1 hour x $35 x 14 patients =
            - $5757.50
    - Upper estimate:
        - [½ hour x $35/hr x (357-14) patients] + 1 hour x $35 x 14 patients =
            - $6492.50
- **TOTAL estimate range for tracking and consent: $128,258-145,443**

- Local MRI read: We estimate that relatively little time (~1/2 hour per MRI) will be required to print out/copy final local MRI report, black out patient identifiers, and write in Center number and subject number. These documents will then be sent to RTI.
    - Lower estimate: ½ hour x $35 x 400 MRI's = $7000
    - Upper estimate: ½ hour x $35 x 450 MRI's = $7875
- **TOTAL estimate range for obtaining local MRI read: $7000-7875**

- Training and assuring reliability: The first enrolled SUPPORT Neuroimaging cohort patient will reach the 6th birthday in May 2011. However, given the length of the SUPPORT trial (enrollment expected to be complete early 2009), the final enrolled patients will have 6-7 year follow-up windows that extend from early 2015 to early 2016. Thus, the total cohort follow-up period will span from May 2011 through early 2016. To ensure ongoing training and achieve the best possible reliability for the primary outcome measure (WPPSI-III), we have made the revisions outlined below.
    - Training sessions: We propose adding another WPPSI-III training session for all sites midway through the follow-up (sometime during 2013). As with the Extended Hypothermia Follow-up, these training sessions will also include training in other components of the follow-up exam, including the NEPSY and PEDI. 15 sites are now participating in the SUPPORT Neuroimaging secondary, but the 15th site (Emory) will not have patients reaching the 6th birthday until after 2013. We have also added incrementally to the cost per site in 2013 to adjust for inflation.
        - First training session (prior to May 2011): $3200 x 14 sites = $44,800
        - Second training session (mid-2013): $3400 x 15 sites = $51,000
    - Reliability assessment: In response to Subcommittee comments, we propose ongoing routine exam taping to be sent from participating sites to one of two GOLD STANDARD WPPSI-III psychologists. We propose that,

after training and subsequent certification by one taped exam on a non-study patient, the first 3 exams from each site be taped and sent for review and comment, then every 10th exam. This approach will necessitate a DVD recorder to be purchased by each site. We estimate that 3 hours will be required to review and comment upon each WPPSI-III exam at $60/hour. Gold standard psychologists will assure that turn-around for comments on these exams be rapid so that sites can incorporate feedback in subsequent scheduled patients' visits. Thus, the budget would reflect the following:

- DVD recorders for each site: $350 x 15 sites = $5250
- Review and comment on certification exam =
  - 1 x 15 sites x 3 hours x $60/hr = $2700
- Review 1st 3 exams from each site =
  - 3x15 site x 3 hrs x $60/hr = $8100
- Review of every 10th exam: Dependent on follow-up numbers:
  - If total 357 patients (upper limit) = 30 additional exams x 3 hrs x $60/hr = $5400
  - If total 315 patients (lower limit) = 26 additional exams x 3 hrs x $60/hr = $4680

- **TOTAL estimate – training/consistency assessments: $116,530 - $117,250**

- 6-7 year visit costs:
  - $1000/visit
  - Lower estimate: 315 patients X$1000=$315,000
  - Upper estimate: 357 patientsX$1000=$357,000
- **TOTAL estimate for final visit costs: $315,000-$357,000**

TOTAL BUDGET ESTIMATE: $566,788 - $627,568

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From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT follow up
Date: Thursday, October 23, 2008 4:28:11 PM
Attachments: MockPatientTrackingContacts.doc
MockSiteTrackingList copy.xls
ProposedTrackingQuestion.doc

Though it Iowa if just preparing for their IRB submission, these proposed mock contact and tracking tools may help.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 4:13 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

We have SUPPORT and FU already in place. I can see if Susan is close on the protocl

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, October 23, 2008 4:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

Would the IRBs buy it without a protocol in place?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 4:06 PM
To: Zaterka-Baxter, Kristin; Das, Abhik
Subject: FW: SUPPORT follow up

Can this be accomplished with a technical memo? I suspect it will come up at other sites, or should we push to get the protocol finalized?

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Thursday, October 23, 2008 4:02 PM
To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Cc: Johnson, Karen
Subject: FW: SUPPORT follow up

Susan, Rose, or Stephanie,
Can you help us with what to provide the IRB about the plan to contact families for the 6-7-yr follow-up.
Thanks,
Ed

that you have received the message in error, then delete it. Thank you.

From: Johnson, Karen
Sent: Thursday, October 23, 2008 2:39 PM
To: Bell, Edward
Subject: RE: SUPPORT follow up

Ed,
I am going to submit this to the IRB along with an increase in the compensation for follow-up and the latest DSMC report. Is there a more official notice about the request to re-contact the family for the 6-7 year FU study? I anticipate our IRB having an issue with asking parents if we can continue to contact them without a solid plan in place.
KJ

From: Bell, Edward
Sent: Friday, February 01, 2008 3:25 PM
To: Johnson, Karen
Subject: FW: SUPPORT follow up
Importance: High

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 01, 2008 3:09 PM
To: rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: nfiner@ucsd.edu; Susan Hintz; Archer, Stephanie (NIH/NICHD) [E]; Newman, Jamie; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: SUPPORT follow up
Importance: High

Hi,
The protocol review committee reviewed the SUPPORT 6-7 year FU study submitted by Susan Hintz today. The subcommittee is requesting revisions and a re-review of the protocol prior to forwarding to the steering committee. There is significant enthusiasm for this study. In the meantime, the committee is asking that sites seeing patients in follow up who have had the neuroimaging studies done as a secondary to the SUPPORT Trial to **request permission to re-contact the family** in the event that the 6-7 year FU study goes forward.

Let me know if there are any questions.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
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Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

Patient Tracking Tool

6-7 year SUPPORT Follow-up

Red items: RTI provides

Name MR # 3rd birthday _____

Study # _____ DOB _____ 6th birthday _____

CONTACT LIST:

Contact Name:
Relationship:
Address:
Telephone #'s:
Email:

Contact Name:
Relationship:
Address:
Telephone #'s:
Email:

Contact Name:
Relationship:
Address:
Telephone #'s:
Email:

6-7 Year SUPPORT follow-up SITE TRACKING LIST **Red/bold: RTI data**; italic:site data

Patient Name	*MR #*	**Study #**	**DOB**	**18 months**	**22.5 months**	*month status*	**3 years**	**4 years**	*3-4 year status*	**6 years**	**7 years**	*6-7 year status*
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	
		###	Date	Date	Date		Date	Date		Date	Date	

Tracking Question Form at 4 years

6-7 year SUPPORT Follow-up

Sites to be queried for each subject enrolled in SUPPORT Neuroimaging and Neurodevelopmental Outcomes secondary, with successful near-term MRI, and discharged from hospital alive:

Subject # _____ is now 4 years of age:

Were you able to contact the family? __ __ __ __ __ __ __ (code all that apply)

1. Yes, saw them in person
2. Yes, spoke on phone
3. Yes, emailed and received reply
4. No, left voicemail(s) at number that was definitely still the family's and have not heard back
5. No, left generic voicemail(s) at number that might not be the family's and have not heard back
6. No, sent mail to last known address and it was returned
7. No, all contact lost. We continue to search
8. Family declines further contact
9. We are planning to see the child at 6-7 years
10. The child is deceased
11. Other _____

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT follow up
Date: Thursday, October 23, 2008 4:24:58 PM
Attachments: REVISEDFollow6_7yearNeuroSUPPORT.DOC

Would it be up to the individual sites to devise a plan for contact for their population; I don't see any contact or specific tracking sections in the protocol proposal from last Feb.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 4:13 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

We have SUPPORT and FU already in place. I can see if Susan is close on the protocl

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From: Das, Abhik [mailto:adas@rti.org]
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To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT follow up

Would the IRBs buy it without a protocol in place?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 4:06 PM
To: Zaterka-Baxter, Kristin; Das, Abhik
Subject: FW: SUPPORT follow up

Can this be accomplished with a technical memo? I suspect it will come up at other sites, or should we push to get the protocol finalized?

From: Bell, Edward [mailto:edward-bell@uiowa.edu]
Sent: Thursday, October 23, 2008 4:02 PM
To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Cc: Johnson, Karen
Subject: FW: SUPPORT follow up

Susan, Rose, or Stephanie,
Can you help us with what to provide the IRB about the plan to contact families for the 6-7-yr follow-up.
Thanks,
Ed

From: Johnson, Karen
Sent: Thursday, October 23, 2008 2:39 PM
To: Bell, Edward
Subject: RE: SUPPORT follow up

Ed,
I am going to submit this to the IRB along with an increase in the compensation for follow-up and the latest DSMC report. Is there a more official notice about the request to re-contact the family for the 6-7 year FU study? I anticipate our IRB having an issue with asking parents if we can continue to contact them without a solid plan in place.
KJ

From: Bell, Edward
Sent: Friday, February 01, 2008 3:25 PM
To: Johnson, Karen
Subject: FW: SUPPORT follow up
Importance: High

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 01, 2008 3:09 PM
To: rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: nfiner@ucsd.edu; Susan Hintz; Archer, Stephanie (NIH/NICHD) [E]; Newman, Jamie; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie
Subject: SUPPORT follow up
Importance: High

Hi,
The protocol review committee reviewed the SUPPORT 6-7 year FU study submitted by Susan Hintz today. The subcommittee is requesting revisions and a re-review of the protocol prior to forwarding to the steering committee. There is significant enthusiasm for this study. In the meantime, the committee is asking that sites seeing patients in follow up who have had the neuroimaging studies done as a secondary to the SUPPORT Trial to **request permission to re-contact the family** in the event that the 6-7 year FU study goes forward.

Let me know if there are any questions.

Thanks
Rose

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Extended follow-up at 6-7 years of age of patients enrolled in the Neuroimaging and Neurodevelopmental Outcome Secondary to SUPPORT

Proposal Subcommittee (*Final Subcommittee may include others*):

Susan Hintz, M.D., M.S. Epi.
Betty Vohr, M.D.
Maureen Hack, M.D.
Neil Finer, M.D.
W. Kenneth Poole, Ph. D.
Jane Hammond, Ph.D.
Abhik Das, Ph.D.
Seetha Shankaran, M.D.
M. Bethany Ball, M.S.
Rosemary Higgins, M.D.

I) ABSTRACT:

The NICHD NRN SUPPORT Neuroimaging cohort will be the largest cohort of extremely preterm infants with brain magnetic resonance imaging (MRI). Children born extremely prematurely continue to have significant neurodevelopmental challenges in later childhood; many subtle yet significant cognitive and performance problems cannot be delineated until 5-8 years and beyond. Early and accurate prediction of neurodevelopmental outcome would be invaluable, but cranial ultrasound (CUS) and other early variables do not reliably predict outcomes. White matter (WM) injury has been strongly implicated in both neuromotor and cognitive impairment, and a developmental neuroanatomical link between WM injury and gray matter disruption appears to exist. MRI is better than CUS in identifying subtle and diffuse WM injury, as well as cerebellar, and gray matter abnormalities. Small and larger studies to date, including the 2-year New Zealand premie MRI cohort results, have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities. But a significant association of MRI abnormalities with cognitive impairment at 18-24 months has not yet been reported. However, subtle neonatal MRI abnormalities may predict cognitive problems in early school age that cannot be delineated in very early childhood. **We propose a 6-7 year neurodevelopmental follow-up of the SUPPORT Neuroimaging cohort to test the hypothesis that neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment and disability at 6-7 years. We will also assess whether injury severity on neonatal MRI will be associated with longitudinal cognitive and disability level changes. In addition, we will examine the frequency of cognitive impairment and disability between ventilatory or oxygenation saturation SUPPORT intervention groups.** The SUPPORT Neuroimaging cohort is valuable and unique among other worldwide premie MRI cohorts; by undertaking 6-7 year follow-up, the NICHD NRN is in an outstanding position to substantially contribute to the understanding of the later outcomes of extremely preterm infants and their prediction.

Hypotheses: Among <28-week EGA children enrolled in the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary, surviving to hospital discharge:

PRIMARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting cognitive impairment (WPPSI-III IQ<70) at 6-7 years

SECONDARY:

- Neonatal brain MRI will be superior to neonatal CUS in predicting disability at 6-7 years
- There will be insufficient evidence to reject the null hypothesis that no differences exist in the frequency of cognitive impairment or disability between ventilatory or oxygenation saturation SUPPORT intervention groups in this sub-cohort.
- Neonatal brain MRI will be superior to neonatal CUS in predicting CP at 6-7 years.
- Neonatal brain MRI will be superior to neonatal CUS in predicting mild-moderate cognitive impairment (WPPSI-III 1-2 SD below population mean) at 6-7 years

- Injury severity on neonatal MRI will be associated with longitudinal cognitive and disability level changes
- Brain injury pattern and topography on neonatal MRI will be associated with anatomic and functional type of CP

Specific Aims:

- To assess cognitive, neuromotor, functional and behavioral outcomes of the SUPPORT Neuroimaging cohort at 6-7 years of age
- To examine the independent associations of neonatal neuroimaging findings with neurodevelopmental outcomes
    - Assess the absolute and relative value of early and late neonatal CUS and neonatal MRI, alone and in combination with other risk factors, to predict normal and impaired outcomes
- To examine longitudinal changes in cognitive and overall impairment level from 18-22 month to 6-7 year exams, and assess relationship of neonatal neuroimaging abnormalities and other variables.
- To compare 6-7 year neurodevelopmental outcomes of ventilation and oxygenation SUPPORT randomized groups in this sub-cohort.

II) BACKGROUND AND SIGNIFICANCE:

Long-term neurodevelopmental outcomes of extremely preterm infants:

Despite advances in perinatal and neonatal management and improvement in survival, short-term neurodevelopmental outcomes of extremely preterm and extremely low birth weight (ELBW) infants appear to remain guarded (Vohr, Hintz, Costeloe). This reported high frequency of disability in very early childhood (18-24 months) makes longer-term neurodevelopmental outcome studies crucial. Evaluation at a later age allows identification and delineation of a broader range of problems, including cognitive delay, more subtle motor disabilities, and behavioral problems to be determined. It also allows for assessment of the strength of perinatal and neonatal variables as potential predictors of long-term outcome, and for longitudinal analysis to determine the predictive value of early disability.

Later childhood follow-up studies have demonstrated that significant neurodevelopmental and cognitive impairment continue. In the 206 ELBW infants followed at 5 years in the Finnish National Cohort (Mikkola), 20% had major disabilities, and 19% of those <27 weeks were diagnosed with cerebral palsy (CP). The EPICure Study Group (Marlow) reported on 241 <26 week survivors at 6 years; severe overall cognitive delay was present in 21% compared with test norms (41% compared with term controls), and disabling CP was diagnosed in 13%. In a study of 219 ELBW infants 8 years (Hack), Hack, et. al. reported CP in 14%, severe cognitive impairment in 15%, moderate-severe cognitive impairment in 38%, and significant motor skills problems in 27%. Families reported substantial functional limitations, including emotional delay, trouble understanding or communicating, and need for medication or equipment; needs for special services were significantly greater than for the normal birth weight (NBW) control group. Impairment in academic (32%) and adaptive skills (48%) have also been reported among ELBW children, and are significantly more frequent than in NBW controls (Taylor). In an ELBW or <28 week EGA cohort at 8 years

(n=275), Anderson, et. al. reported significant impairment across all tested cognitive and educational abilities compared with NBW controls (Anderson).

Summary: Children born extremely preterm or ELBW continue to have substantial motor and cognitive disabilities in childhood, as well as more subtle functional and adaptive impairments. Delineation of some of these problems may not even be reasonably undertaken until 5-8 years of age. The true impact of these impairments may not be felt until later school age (Saigal).

Predicting neurodevelopmental outcome: Neonatal CUS and other variables:

CUS and short-term (18-24 months)

The association of a combination of severe neonatal CUS abnormalities and adverse short-term neurodevelopmental outcome has been reported in numerous studies (Vohr, Hack#2). But, even in the most detailed CUS studies, the strength of this association appears to be consistent primarily for combined endpoints, or for CP or motor disability, but not for pure cognitive delay (deVries, Hack #2, Wood). In addition, severe CUS abnormalities are not uniformly predictive of adverse short-term outcome and normal CUS do not predict normal outcome in this high-risk population (deVries, Hack#2, Laptook, Ancel, Pinto-Martin). In fact, in a predictive modeling analysis, Ambalavanan found that severe grade of IVH explained only 8% of the variance in low MDI and 5% of the variance for major handicap at 18-22 months (Ambalavanan).

CUS and long-term outcome (5-8 years)

Reported associations of neonatal CUS findings and long-term outcomes are inconsistent. Sherlock, et. al. (Sherlock) reported that neurodevelopmental impairment at 8 years varied little with increasing severity of IVH; a trend for worse cognitive and neurosensory outcome with higher grade IVH explained solely by the outcomes of the small number of patients with parenchymal hemorrhage. Similarly, 6-year results of the Neonatal Brain Hemorrhage Study (NBHS) showed that 88% of LBW patients with germinal matrix or IVH had normal cognitive outcomes (Whitaker).

Nevertheless, several analyses have reported abnormal neonatal CUS to be "significantly associated with" adverse long-term neurodevelopmental outcomes in ELBW cohorts. For instance, Mikkola found an association of abnormal CUS with CP and IQ at 5 years (Mikkola), and Taylor found an association of abnormal CUS with executive function and memory on the NEPSY (Taylor). However, the definition of CUS "abnormality" varies among studies, with some analyses including markers of white matter injury (PVL or ventricular enlargement (VE)) and others limiting only to IVH. In addition, a finding of association does not specifically address the independent *predictive* power of neonatal CUS, particularly with respect to cognitive outcome in later childhood. In fact, Hack, et. al. demonstrated that only 36% of those with a Mental Processing Composite (MPC) of <85 at 8 years had had an abnormal CUS, and only 45% of those with MPC<70 (Hack #3). In the 6-year follow-up of the NBHS cohort, only 12% of those with GM/IVH had borderline IQ or mental retardation (Whitaker). In that study, PVL/VE was separately assessed; this revealed a stronger 56.5% of those with PVL/VE had borderline IQ or mental retardation. This may be a clinical insight to the importance of white matter (WM) injury for longer-term adverse outcomes *including cognitive outcomes*. Nevertheless, more that 40% of patients with PVL/VE had normal

intelligence at 6 years - a finding, which, in turn, may serve to underscore the inability of routine CUS to see anything more subtle than the most definitive WM injury.

Other potential predictors of long-term neurodevelopmental outcome:

Investigators have attempted to determine other, more reliable predictors of longer-term outcomes of preterm infants. Doyle reported on prediction of survival free of major disability at 5 years among the surviving VICS cohort on the basis of the number of "adverse neonatal variables" (Doyle). Although observed and predicted values were similar, the outcome was not specifically focused (i.e., combined neurologic/neurosensory/cognitive endpoint), the observed 95% CI range was broad for 2 and 3 variable groups, and the patient numbers were quite small. Others have assessed the predictive value of *earlier neurodevelopmental findings*. Marlow found that only severe disability at 30 months was highly predictive of 6-year outcome; 38% of children defined as mild or moderately disabled and 24% with "no disabilities" had moderate or severe disabilities at 6 years. Hack (#3) found the positive predictive value of MDI<70 at 20 months for MPC<70 at 8 years to be extremely poor (PPV=0.37). However, some intriguing links of longitudinal decline in cognitive ability with brain injury have been reported. In follow-up to the I-IVHP trial, Ment found that cognitive scores declined from 36 to 96 months only in the subset of patients with early IVH coupled with PVL or VE (Ment). Also from the I-IVHP trial, the presence of spastic cerebral palsy at 3 years was more strongly predictive of IQ<70 at 8 years than was cognitive testing at 3 years (Pleacher). These findings are not surprising, in part due to the potential mechanism linking white matter injury with reduced connectivity, gray matter loss, and cognitive delay.

Summary: Aggregate abnormal findings on neonatal CUS do not reliably predict either short- or long-term neurodevelopmental outcomes, although markers of WM injury appear to be stronger links. Early cognitive measures also do not predict later cognitive outcome well in most circumstances. These findings emphasize the deficits of routine CUS to detect subtle injury, and also underscore the poor predictive validity of early cognitive measures for later cognitive outcomes (Aylward).

MRI: Delineation of injury and predicting outcomes

Imaging injury:

MRI provides a more complete and anatomically detailed evaluation of the neonatal brain. Studies comparing the relative capabilities of US with MRI to detect brain injury among preterm infants in the newborn period have concluded that MRI detects white matter injury better than CUS (Maaloof, Childs), and provides additional information on brain development not noted by cranial US. Studies have also demonstrated that subtle and diffuse WM injury, not detectable by CUS, may be common among preterm infants at term (Counsell).

White matter injury and cognitive outcome:

Cognitive delay is a significant and difficult to predict component of the range of impairments. Recent studies have demonstrated that white matter injury in the preterm infant is associated with both reduced cortical gray matter volume, and with reduced deep gray matter volume by MRI at term equivalent age (Inder, Boardman). There are several potential mechanistic pathways, including via direct axonal or subplate neuron

injury, that may explain this finding. The common endpoint is reduced connectivity, limited neuronal differentiation, and poor cognitive outcome. In fact, recent research using MRI tractography in a series of former preterm infants at approximately 2 years of age has provided evidence for this theory of reduced cortical and thalamic connections after WM injury (#2 Counsell).

MRI in preterm infants and early neurodevelopmental outcome

After early studies suggesting that MRI at near term was a more powerful predictive tool than CUS for short-term neurodevelopmental outcome (Valkama, Roelents-van-Rijn, Mirmiran), larger MRI studies were undertaken. Many have been single-center efforts, focused chiefly on the association of early neurodevelopmental outcomes with MRI findings in preterm infants at term and earlier, and without extensive comparison of the predictive validity of MRI and CUS. Among these, Miller, et. al. (UCSF, <34 weeks EGA, 86 survivors) and Dyet, et. al. (Hammersmith, <30 weeks EGA, 119 survivors) described MRI findings from birth through near-term and found that WM injury, particularly diffuse injury, was common and was associated with adverse neurodevelopmental outcomes. Cerebellar injury, not easily seen with routine CUS, was also a prognostic indicator of poor outcome. Of importance, although MRI data were meticulously obtained, only 66% of the group had complete follow-up data.

However, other groups have preterm/MRI cohorts, with research aims that include comparison of predictive capabilities of MRI and CUS.

- The recently reported 2-year neurodevelopmental outcomes of the New Zealand (NZ) cohort (Woodward) (<30 weeks EGA, 167 survivors) revealed that 1) presence of moderate-severe WM abnormalities on MRI was significantly associated severe motor delay and cerebral palsy, independent of CUS abnormalities and other risk factors; 2) a significant correlation between white and gray matter abnormalities; 3) although increasing severity of WM injury was associated with worse Bayley MDI scores, an independent association of moderate-severe WM injury with severe cognitive delay was not reached. Although sensitivity of moderate-severe WM to predict CP (65%), neurosensory impairment (82%) and severe cognitive delay (41%) was improved over abnormalities on CUS (18%, 16%, and 15%, respectively), the total number of the cohort with moderate (n=29) or severe (n=6) WM injury was small, and approximately half of those did not have neurodevelopmental impairment.
- The 2-years results of the Australian cohort (<1250 g or <30 weeks EGA, n=221) were reported at the 2007 PAS (Hunt). "Major" white matter injury was found to be a more significant independent risk factor than PVL for CP, and was an independent risk factor for neurosensory disability where PVL was not. IVH grade 4 was not found to be a significant risk factor for either outcome.
- **SUPPORT Neuroimaging cohort:** Continuing enrollment; first enrolled birth date 5/10/05. Follow-up at 18-22 months ongoing.

SUPPORT Neuroimaging cohort: Unique and valuable

The SUPPORT Neuroimaging cohort, estimated to include 400-450 survivors with complete CUS and MRI data by the time SUPPORT enrollment closes, will be the largest preterm/MRI/follow-up cohort worldwide. This cohort is also a higher-risk group than other cohorts, and thus innately targets the most important outcomes group. Follow-up at 18-22 months is in progress, with the first enrolled SUPPORT Neuroimaging patient follow-up window 2/6/07-6/21/07. The SUPPORT Neuroimaging

cohort is inherently exceptional and unique in that it was developed within a randomized controlled trial. Thus, the management profile of a crucial neonatal care component has been more carefully controlled and monitored than would otherwise be the case. This also allows for secondary analyses of the association of respiratory management strategies with subtle MRI findings and outcome. The SUPPORT Neuroimaging cohort also has a number of advantages over other preterm/MRI cohorts:

1) New Zealand (NZ) cohort:
    a. Setting: SUPPORT: Embedded in a randomized controlled trial within a multicenter network with focused neurodevelopmental follow-up priorities; NZ: two centers one in New Zealand another in Melbourne, Australia, with a primary focus on MRI imaging
    b. EGA/risk profile:
        i. SUPPORT: <28 weeks EGA; NZ cohort: <30 weeks. Only 87/167 of the NZ cohort was <1000 g BW, and 95/167 were <28 weeks.
    c. Cohort size: SUPPORT: estimated 400-450 survivors; NZ: 167 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. SUPPORT: Two specifically-timed and required CUS, including near-term; NZ: within 2 days, 5-7 days, 4-6 weeks; if "abnormality" detected, more frequent performed.
        ii. SUPPORT: central reader, detailed central reader data instrument; NZ: No central reader. "Worst" CUS findings recorded only with respect to PVL/echolucency, grade 3 or 4 IVH
    e. Timing/interpretation of MRI:
        i. BOTH: Near-term
        ii. BOTH: Central reader
        iii. SUPPORT: detailed MRI central reader form; NZ: central reader data collection instrument not known, but MRI abnormality categories broad.
    f. Non-imaging data collection:
        i. SUPPORT: extensive, including detailed respiratory data; NZ: less detailed
2) Australia cohort:
    a. Setting: Single center in Melbourne, Australia
    b. EGA/risk profile:
        i. <30 weeks, <1250 g.
    c. Cohort size: 221 survivors at 2 years.
    d. Timing/interpretation of CUS:
        i. Not required, retrospectively gather information (communication, Rod Hunt).
        ii. "Worst" CUS findings gathered - PVL, grade 4 IVH
    e. Timing/interpretation of MRI:
        i. Near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine

3) Hammersmith cohort:
    a. Setting: Single center
    b. EGA/risk profile:
        i. <30 weeks.
    c. Cohort size: 119 survivors at 2 years. **Note: complete follow-up data were available for only 66% of the group**
    d. Timing/interpretation of CUS:
        i. CUS not focus – studies thus far report MRI
    e. Timing/interpretation of MRI:
        i. MRI serial – from birth to near-term
        ii. Central reader
    f. Non-imaging data collection:
        i. Routine
4) UCSF:
    a. Small, single center
    b. <34 weeks
    c. 86 survivors at 2 years
    d. CUS not focus – MRI's serial from birth to near-term
    e. Non-imaging data routine

Summary: MRI is better than CUS in identifying subtle and diffuse white matter injury, which is relatively common among preterm infants at term, as well as cerebellar, and gray matter abnormalities. Earlier small studies suggested that MRI better predicts adverse neuromotor outcome than CUS. Two-year results of the NZ cohort have shown WM injury by MRI to be significantly associated with CP and adverse neurosensory outcome independent of CUS abnormalities, but not with adverse cognitive outcome. The extent to which these findings will be enhanced and clarified, and how or when MRI should be applied in routine clinical practice, awaits the 18-22 month results of the larger, higher-risk SUPPORT Neuroimaging cohort. However, a biologic mechanism for the link between WM injury and cognitive impairment exists. Early cognitive findings are poor predictors of later challenges, and subtle neonatal MRI abnormalities may predict subtle problems in early school-age that cannot be delineated at 18-22 months.

Later outcomes: Need for SUPPORT Neuroimaging extended follow-up

Evidence for altered brain development: corroboration of need for long-term follow-up

Short-term neurodevelopmental outcomes are only a tiny window into the future of a former preterm child. Difficulties in cognition, performance, verbal/language skills, attention and behavior may not be delineated until later ages. There are also data to support the concept that even minor, undiagnosed brain injury sustained preterm infant is associated with disordered brain development. The degree of white matter injury purported to be associated with reduced connectivity and subsequent gray matter reduction may be subtle, and its effects dependent on other variables (Inder, Boardman). Rademaker, et. al. found that even minor differences in lesion severity on MRI performed at 8 years of age in <32 week EGA appeared more accurate in prediction of IQ and total impairment score than neonatal CUS (Rademaker). These findings may suggest that subtle injury could have been seen on *neonatal* MRI, which in turn, could have aided in prediction. In a DTI and volumetric MRI study, Yung

demonstrated that *neurologically normal* LBW preterm infants at 8-12 years had significantly reduced WM volumes than term controls, and that this was significantly related to reduced IQ (Yung). This finding again suggests that early WM injury leading to reduced volume may have been identifiable on neonatal MRI. Kesler, et. al. described high-resolution MRI results from 73 preterm and 33 term infants at 7-11 years of age; preterm infants had disorganized cortical development, potentially involving disrupted neural migration (Kesler).

Importance of SUPPORT Neuroimaging secondary long-term follow-up

The importance of long-term follow-up for any preterm cohort with neonatal MRI's is clear.

- Our current ability to predict later childhood outcomes from perinatal and neonatal variables is limited. The prognostic validity of neonatal CUS findings is limited. Even early childhood neurodevelopmental outcome, apart from severe impairment, do not accurately predict later childhood neurocognitive outcome. MRI holds promise as a better predictive modality, but neonatal MRI has not been evaluated with respect to truly long-term outcomes.
- Performance skills are different at 18-22 months than 6-7 years; assessments at the later age may uncover subtle, yet significant problems, which may be associated brain injury seen by neonatal MRI.
    - Such assessments may reveal attention/behavior problems, language and verbal delays, more detailed picture of cognitive/academic impairment.

But the **SUPPORT Neuroimaging cohort is unique among other cohorts, and is in an outstanding position to substantially contribute to the understanding of neonatal imaging and prediction of long-term neurodevelopmental outcomes**:

- SUPPORT Neuroimaging secondary designed with MRI/CUS predictive comparison in mind, thus careful attention to specifically-timed CUS, detailed central reading of all study neuroimaging
- 18-22 month follow-up is already part of this secondary study
    - Thus, crucial opportunity to evaluate longitudinal changes, and importantly, brain injury patterns or other variables associated with changes in cognitive or functional outcomes
- Prospectively enrolled secondary cohort, embedded within SUPPORT RCT; more consistent management of respiratory approach, comprehensive data collection
    - Opportunity for secondary analyses of randomized ventilation/oxygenation arms of Neuroimaging cohort outcomes at 6-7 years
- Study within the NICHD NRN; neurodevelopmental follow-up is already a focused objective, and follow-up rates have been outstanding for previous trials (Shankaran)
- SUPPORT cohort will be the largest and highest-risk cohort of premature infants with CUS and MRI. Much has already been invested in this valuable cohort.

In addition, it is important to recognize that other preterm/MRI cohorts, notably the NZ cohort, already have protocols in place for long-term follow-up. The NZ cohort is already beginning 4-5 year follow-up (communication, TE Inder).

Why we can't wait to commit to 6-7 year follow-up:

Finally, it may appear premature to plan for 6-7 year follow-up of this sub-cohort within a RCT that is still enrolling. It may seem reasonable to wait to assess 18-22 month outcome results, and commit to follow-up only after that point. But that approach will not be possible. The birth date of the first SUPPORT Neuroimaging subject was 5/10/2005. If current enrollment rate continues, SUPPORT enrollment will not likely be completed until mid-late 2008. Thus, in the best possible scenario, the final SUPPORT Neuroimaging subject would have an 18-22 month follow-up window *opening* in October-November 2010, while the first SUPPORT Neuroimaging subject will reach the 6th birthday on 5/10/2011. **Therefore, analysis would not be complete for 18-22 month outcomes soon enough to allow for 6-7 year follow-up tracking, planning and preparation.**

III) STUDY DESIGN:

Objective: This is a proposed prospective follow-up study of the 6-7 year neurodevelopmental outcomes of the SUPPORT Neuroimaging Secondary cohort. We will evaluate and compare the capabilities of *neonatal neuroimaging* - CUS and near-term MRI – to predict cognitive impairment, disability, and neuromotor impairment at 6-7 years. We will evaluate longitudinal changes in neurodevelopmental outcome, and assess associated neuroimaging findings and other variables. We will also determine if ventilatory or oxygenation saturation SUPPORT interventions are associated with differences in 6-7 year neurodevelopmental outcomes.

Outcomes:

- Primary: IQ by WPPSI-III<70
- Secondary:
  - IQ score (continuous) by WPPSI-III
  - Disability
    - Severe: Any of: WPPSI IQ >3 SD below mean, severely impaired neuromotor/functional outcome (non-ambulatory, GMFCS level 4-5), profound hearing loss or blindness (not functionally correctable),
    - Moderate: Any of: WPPSI IQ 2-3 SD below mean, moderately impaired neuromotor/functional outcome
    - Mild: Any of: WPPSI IQ 1-2 SD below mean, mildly impaired neuromotor/functional outcome (abnormal neurologic exam, but walking independently, GMFCS level 1-2)
  - Cerebral palsy
    - Classified anatomically and functionally according to Definition and Classification of Cerebral Palsy, April 2006 guidelines
  - Mild cognitive impairment (WPPSI IQ 1-2 SD below mean) and severe cognitive impairment (WPPSI IQ>3 SD below mean)
  - Behavioral and attention deficits

- Chronic conditions and functional limitations

Study population:

- The study population (SUPPORT Neuroimaging cohort) will be comprised of the SUPPORT Neuroimaging and Neurodevelopmental Outcome Secondary enrollees who survived to discharge. **By the time SUPPORT enrollment in completed, it is estimated that 400-450 infants will be in the SUPPORT Neuroimaging cohort.**
- As described in the SUPPORT Neuroimaging and Neurodevelopmental outcome secondary, these patients will have had two CUS (early: 4-14 days of age; late: 35-42 weeks and within 5 days of MRI) and a brain MRI at 35-42 weeks.
  - The CUS with the most severe abnormalities (the "worst" CUS) will be used in comparative analyses
- Estimated cohort size at neurodevelopmental follow-up
  - Follow-up at 18-22 months (ongoing)
    - Estimate 2% death after discharge, 10% loss to F-U: **cohort=350-397 pts**
  - Follow-up at 6-7 years
    - Estimate additional 10% loss to F-U: **cohort = 315-357 pts**

Design:

- This proposed protocol concept is a long-term cognitive, neurologic, and functional follow-up of the SUPPORT Neuroimaging Cohort. **No further neuroimaging is being proposed**.
- Visit at 6-7 years:
  - Neurologic exam and Gross Motor Function exam
    - Diagnosis of CP, type (anatomic description), and severity (Rosenbaum);
    - Gross Motor Function Classification level
    - Fine motor assessment
  - Weschsler Preschool and Primary Scale of Intelligence- III
  - NEPSY
  - ** Pediatric Evaluation of Disability Inventory (PEDI)**
    - For children unable to be tested by the WPPSI and NEPSY due to severe neurodevelopmental impairment
  - Medical history
  - Socioeconomic status (SES)
    - SES data will be assessed by a questionnaire that parallels that of the 18-22 month visit and baseline.
  - Questionnaire for Identifying Children with Chronic Conditions (QUICCC)
  - Attention/behavior instruments:
    - Child Behavior Checklist (CBCL)
    - Conners' Rating Scale
  - Impact on Family questionnaire

Statistical considerations:

- Analyses:

- Since we are concerned with the relative diagnostic power of the MRI versus the CUS, an appropriate statistical methodology is an ROC analysis. This analysis is based on the sensitivity and specificity and compares the diagnostic power over the entire range of the diagnostic variable(s) and thus negates the need to select "cut points". The analysis related to the primary hypothesis will compare the ROC curves for a predictive model based on the MRI data versus a predictive model based on the CUS data. The WPPSI-III < 70 will be the primary outcome variable.
  - We will conduct the ROC analysis with WPPSI-III<70 as the outcome when either MRI or CUS data are in the predictive model and will compare the ROCs for the two models for statistical significance. Since MRI and CUS are done on the same subjects, it will not be necessary to adjust for risk factors in comparing the two tools;
  - We will conduct the ROC analysis with WPPSI-III<70 as the outcome when only traditional clinical variables (non- neuroimaging variables) are the only variables in the model;
  - We will also do the ROC analysis that compares the contribution of MRI and CUS to the prediction of outcome above and beyond that of the traditional clinical variables.
  - Will also do the ROC analysis that compares the incremental value of adding MRI to the prediction of outcome above and beyond that of traditional clinical variables plus CUS
  - Logistic regression analysis will be used to compare 6-7 year neurodevelopmental outcomes between oxygenation and ventilation SUPPORT randomized groups. These analyses will be adjusted for baseline risk variables.
- "Traditional non-neuroimaging variables": Based on previous investigations assessing the associations of demographic, socioeconomic, perinatal, and neonatal factors with school-age outcomes (including Taylor, Doyle #2), we propose the following non-neuroimaging variables will be used in model development; other variables may be considered.
  - Center
  - Gestational age
  - Race
  - Gender
  - Multiple gestation
  - Maternal education level (at baseline)
  - [SUPPORT treatment group]
  - Sepsis or meningitis
  - NEC
  - BPD
  - Postnatal steroids
  - ROP stage III or more severe
  - Length of initial hospital stay (EGA adjusted, i.e., PCA at discharge)

- Any surgery during initial hospitalization

- Sample size and power analysis (Primary Hypothesis):
  - The sample sizes in the table below are based on formulae for two correlated ROCs (e.g. two ROCs based on the same sample). According to the discussion in the protocol above, we assume that around 350 infants will be available for the 6-7 year IQ evaluation. For a two-tailed test at the 0.05 level of significance and assuming the lowest area under the ROC curve (AUC) for the MRI and the CUS is 75%, the 350 infants would produce the powers in the table below for an array of detectable increases in the AUC and prevalence of outcome.

POWER FOR SELECTED INCREASES FROM 75% IN THE AUC OF THE ROC AND PREVALENCES OF THE PRIMARY OUTCOME:
SAMPLE SIZE = 350

AUC Inc. / Outcome P	5%	6%	7%	8%	9%	10%
20%	31%	43%	55%	67%	77%	86%
25%	37%	50%	64%	76%	85%	92%
30%	42%	56%	70%	81%	90%	95%

Hence, if the prevalence of the primary outcome is as low as 20% a sample size of 350 would pick up an AUC increase of 10% with reasonable power (86%); if the prevalence is 30%, the detectable increase would be 8% (with power 80%).

Budget: The costs of this proposed follow-up study would span over several years. The first enrolled patient will reach the 6th birthday on 05/10/2011, and enrollment is still ongoing. **It is estimated that 6-7 year follow-up windows will extend from May 2011 to early 2016.**

- Tracking: Similar to the Extended Follow-up of the Hypothermia Trial, tracking will be important to ensure the best possible follow-up.
  - Between 18-22 month and 3-4 years: 2 phone contacts with tracking
    - 1 hour/contact at $35/hour
    - Lower estimate: 350ptsx2contactsx1 hour eachx$35= $24,500
    - Upper estimate: 397x2x1x$35=$27,790
  - Between 3-4 years and 6-7 years: 4 contacts (q 6 months)
    - 2 hours/contact at $35/hour
    - Lower estimate: 350x4x2x$35=$98,000
    - Upper estimate:397x4x2x$35=$111,160
- **TOTAL estimate range for tracking: $122,500-138,950**

- Training and assuring reliability: The first enrolled SUPPORT Neuroimaging cohort patient will reach the 6th birthday in May 2011. However, given the length of the SUPPORT trial (enrollment expected to be complete early 2009), the final enrolled patients will have 6-7 year follow-up windows that extend from early 2015 to early 2016. Thus, the total cohort follow-up period will span from May 2011 through early 2016. To ensure ongoing training and achieve the best possible reliability for the primary outcome measure (WPPSI-III), we have made the revisions outlined below.
    - Training sessions: We propose adding another WPPSI-III training session for all sites midway through the follow-up (sometime during 2013). As with the Extended Hypothermia Follow-up, these training sessions will also include training in other components of the follow-up exam, including the NEPSY and PEDI. 15 sites are now participating in the SUPPORT Neuroimaging secondary, but the 15th site (Emory) will not have patients reaching the 6th birthday until after 2013. We have also added incrementally to the cost per site in 2013 to adjust for inflation.
        - First training session (prior to May 2011): $3200 x 14 sites = $44,800
        - Second training session (mid-2013): $3400 x 15 sites = $51,000
    - Reliability assessment: In response to Subcommittee comments, we propose ongoing routine exam taping to be sent from participating sites to one of two GOLD STANDARD WPPSI-III psychologists. We propose that, after training and subsequent certification by one taped exam on a non-study patient, the first 3 exams from each site be taped and sent for review and comment, then every 10th exam. This approach will necessitate a DVD recorder to be purchased by each site. We estimate that 3 hours will be required to review and comment upon each WPPSI-III exam at $60/hour. Gold standard psychologists will assure that turn-around for comments on these exams be rapid so that sites can incorporate feedback in subsequent scheduled patients' visits. Thus, the budget would reflect the following:
        - DVD recorders for each site: $350 x 15 sites = $5250
        - Review and comment on certification exam =
            - 1 x 15 sites x 3 hours x $60/hr = $2700
        - Review 1st 3 exams from each site =
            - 3x15 site x 3 hrs x $60/hr = $8100
        - Review of every 10th exam: Dependent on follow-up numbers:
            - If total 357 patients (upper limit) = 30 additional exams x 3 hrs x $60/hr = $5400
            - If total 315 patients (lower limit) = 26 additional exams x 3 hrs x $60/hr = $4680
- **TOTAL estimate – training/consistency assessments: $116,530 - $117,250**

- 6-7 year visit costs:
    - $1000/visit
    - Lower estimate: 315 patients X$1000=$315,000

- Upper estimate: 357 patientsX$1000=$357,000
- **TOTAL estimate for final visit costs: $315,000-$357,000**

TOTAL BUDGET ESTIMATE: $554,030 - $613,200

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From: Finer, Neil
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: School Age Pulmonary Follow up Proposal
Date: Thursday, October 23, 2008 3:27:08 PM

Hi Marie and Rose
Many thanks Marie
I think that this strengthens the idea that if we are doing prolonged follow-up for the MR cohort, we could easily have the same group participate in the breathing outcomes. We have over 400 infants in both!!
Neil

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, October 23, 2008 9:48 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: School Age Pulmonary Follow up Proposal

Numbers as of this week's data (updated last night) are:

MRI: 543
Breathing: 754
Both: 407

Marie

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, October 22, 2008 4:33 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: School Age Pulmonary Follow up Proposal

Marie
Can you tell how many are enrolled in both?
Thanks
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 22, 2008 11:54 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: School Age Pulmonary Follow up Proposal

Here are the number of infants enrolled in the secondaries.

Number patients enrolled in MRI: 543
Number patients consented to Breathing Outcomes: 751

Marie

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 21, 2008 5:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: FW: School Age Pulmonary Follow up Proposal

Rose
Could you send this proposal so the SUPPORT Subcommittee. Richard and I think is a good protocol. I would like the committee to review and then we could discuss on a conference call before the Jan meeting. I would like to invite Tim to discuss this that meeting if the Subcommittee is interested. I think we may have a large number of infants in both the MRI and Breathing outcomes and thus longer follow-up including PFTs may make good fiscal sense. Could Marie figure out how many infants are enrolled in both of these secondaries?
Many thanks
Neil

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Sunday, September 14, 2008 5:47 PM
To: richard.ehrenkranz@yale.edu; Finer, Neil
Subject: School Age Pulmonary Follow up Proposal

Hi Richard and Neil,

Attached is a first draft of a proposal entitled, SUPPORT – School Age Breathing Outcomes Study. The goals of the proposal are to determine whether the pulmonary effects of SUPPORT are sustained to school age by measuring pulmonary function of SUPPORT patients at 6-7 years of age. As a major secondary goal, the proposal describes studies to determine whether the pulmonary benefits of SUPPORT reduce reaction or susceptibility to secondary pulmonary insults such as environmental tobacco smoke, infections and inhaled allergens during childhood. Together these goals have potential to substantially increase our understanding of pulmonary morbidity among extremely preterm infants.

Please let me know your thoughts.

Thanks

Tim Stevens

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From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, October 23, 2008 12:36:06 PM

Sure - I've passed the request to Ruth.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 23, 2008 12:24 PM
To: sduara@miami.edu
Subject: FW: SUPPORT

Shahnaz
Two of the four infants below are still showing up as ROP pending.

8	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
8	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.

Can they be marked as "N?" see below

Thanks
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, August 25, 2008 12:35 PM
To: Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Everett-Thomas, Ruth; Phelps, Dale
Subject: RE: SUPPORT

You are correct that the infants below were marked "Final acute status lost to follow-up at 55 weeks PMA." Doing so will stop the missing outcomes reports from being generated until the child reaches follow-up age. However, a month before the FU window opens we send messages to remind the centers to obtain final ROP status at the FU exam (assuming the child is seen for FU). If the child is still lost and the FU exam will not take place, then the SUPP10 field "Final ROP status determined at 18M follow-up" should be marked "N" and these reminders will also stop. Let me know if you have any additional questions.

Thanks,
Marie

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From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Monday, August 25, 2008 12:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; Everett-Thomas, Ruth; Phelps, Dale
Subject: RE: SUPPORT

Hi Rose,

We though this was laid to rest. These 4 infants never returned to our center for follow-up eye care and have not been locatable – they need to be considered 'lost to follow up'. Ruth and I explained this at length last year and Dale very kindly took Ruth step-by-step through the process that would allow the record to reflect this. I'm not sure why this is popping up again.

We are all fine – hope the same goes for the NRN.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 12:06 PM
To: Duara, Shahnaz
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT Outcomes. Let us know how you are doing.

Thanks for all the hard work!!!!

Rose

CENTER	NETWORK	ROP_message
8	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.

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

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT missing outcomes
Date: Thursday, October 23, 2008 11:44:42 AM
Attachments: RE SUPPORT.msg

They responded in August that the infants were lost to FU, and I responded that they needed to mark the SUPP10 field "Final ROP status determined at 18M follow-up" with "N" to stop receiving reminders. However, for two children they marked "Final ROP status determined at 18M follow-up"="Y." They need to change that answer to "N."

Marie

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:41 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: RE: SUPPORT missing outcomes

Did Miami tell us the last time that their two infants with missing ROP outcomes don't have status?

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, October 20, 2008 6:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes

Rose,

Attached is the list of SUPPORT infants with missing outcomes this month.

Marie

Marie Gantz, Ph.D.
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From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; Rich
Subject: Re: SUPPORT
Date: Thursday, October 23, 2008 11:05:23 AM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> We are missing a few outcomes for SUPPORT. Let us know how you are doing.
>
> Thanks for all the effort!!
> Rose

CENTER	NETWORK	BPD_message
13	(b) (6)	Infant was eligible for challenge (per PHY01) but outcome was not entered on PHY02RA

Rosemary D. Higgins, MD
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Hi Rose, the outcome was not entered but it has been now. The baby did not pass the challenge.
Monica

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu; "nancy newman"; drfjcmd@aol.com
Subject: RE: SUPPORT outcomes
Date: Thursday, October 23, 2008 10:03:01 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:03 PM
To: mcw3@cwru.edu; nancy newman; Bonnie Siner; drfjcmd@aol.com
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT outcomes

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.
Given your outstanding recruitment, this low number is truly exemplary!!!!
Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.-already entered
3	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.-waiting for report.
3	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age. -waiting for report.
CENTER	NETWORK	FU_message
3	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed-Bayley was just completed by home visit; will be entered next week.

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From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B; Hamer, Faithe Angeline
Subject: RE: SUPPORT
Date: Wednesday, October 22, 2008 5:29:04 PM

They did not consent for breathing outcomes. I have requested they be removed and have on my list to double-check that this is done. The death was post-discharge. I will f/u on the NF-12 3 b. Thanks

Leslie Dawn Wilson, RN, BSN
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317.312.(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:34 PM
To: Wilson, Leslie Dawn; Poindexter, Brenda B
Cc: Das, Abhik; Marie Gantz
Subject: RE: SUPPORT

So they did not consent for breathing outcomes, correct? If so, those forms should be deleted. Was the death an in-hospital or post-discharge death? If in-hospital, it should get reflected on GDB. If post-discharge, we will need the NF-12 3.b filled out.

Thanks
Rose

From: Wilson, Leslie Dawn [mailto:ldw@iupui.edu]
Sent: Wednesday, October 22, 2008 4:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Das, Abhik; Marie Gantz
Subject: RE: SUPPORT

Hi. This infant passed away(b) (6) For Breathing Outcomes, there was a SUPP01, 02, and 03 completed, stating that the interviews were not done because of the death. I had requested that even this be removed from the network database as there was no consent obtained for pt to ever be in this sub-study.

Thank you-leslie

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317.312.1121 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 22, 2008 4:14 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Marie Gantz
Subject: SUPPORT

Hi,
We are missing a few outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the effort!!
Rose
CENTER

NETWORK

FU_message

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FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: FW: School Age Pulmonary Follow up Proposal
Date: Tuesday, October 21, 2008 5:27:46 PM
Attachments: SUPPORT - School Age Breathing Outcomes Proposal 9-12-08.doc

Rose
Could you send this proposal so the SUPPORT Subcommittee. Richard and I think is a good protocol. I would like the committee to review and then we could discuss on a conference call before the Jan meeting. I would like to invite Tim to discuss this that meeting if the Subcommittee is interested. I think we may have a large number of infants in both the MRI and Breathing outcomes and thus longer follow-up including PFTs may make good fiscal sense. Could Marie figure out how many infants are enrolled in both of these secondaries?
Many thanks
Neil

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Sunday, September 14, 2008 5:47 PM
To: richard.ehrenkranz@yale.edu; Finer, Neil
Subject: School Age Pulmonary Follow up Proposal

Hi Richard and Neil,

Attached is a first draft of a proposal entitled, SUPPORT – School Age Breathing Outcomes Study. The goals of the proposal are to determine whether the pulmonary effects of SUPPORT are sustained to school age by measuring pulmonary function of SUPPORT patients at 6-7 years of age. As a major secondary goal, the proposal describes studies to determine whether the pulmonary benefits of SUPPORT reduce reaction or susceptibility to secondary pulmonary insults such as environmental tobacco smoke, infections and inhaled allergens during childhood. Together these goals have potential to substantially increase our understanding of pulmonary morbidity among extremely preterm infants.

Please let me know your thoughts.

Thanks

Tim Stevens

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SUPPORT - School Age Breathing Outcomes Study

A Proposal for the NICHD Neonatal Research Network

September 12th, 2008

Timothy P. Stevens, MD, MPH

Richard A. Ehrenkranz, MD

Neil N. Finer, MD

Proposal Date: September 12, 2008

Contact Information:
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Synopsis: For SUPPORT– Breathing Outcomes Study patients, we propose to extend pulmonary follow-up through and perform pulmonary function testing at 6-7 years of age. Longer term, longitudinal pulmonary follow up of SUPPORT patients will provide important data on three critical outcomes of the Trial, 1) do the SUPPORT Trial interventions, management with high vs. low oxygen saturation targets and early CPAP vs. prophylactic surfactant and ventilation, result in improved lung function, reduced respiratory symptoms and less need for pulmonary care at 6-7 years of age; 2) do the pulmonary benefits of SUPPORT reduce reaction or susceptibility to secondary pulmonary insults such as lung irritants, infections and allergens during childhood; and 3) are the pulmonary benefits of SUPPORT observed at 18-22 months of age sustained during childhood, thus improving pulmonary function and reducing respiratory symptoms and use of health services for pulmonary care among extremely preterm infants at 6-7 years of age. The primary outcome will be comparison of the FEV_1 ratio (ratio of forced expiratory volume in 1 s divided by that predicted based on the patients weight, height and sex) for infants in each of the four SUPPORT treatment groups at 6-7 years of age. Important secondary outcomes will include forced vital capacity (FVC), forced midexpiratory flow rate (FEV25-75), ratio of FEV1 to FVC (FEV%), peak expiratory flow velocity (PEF) and prevalence of symptomatic airway dysfunction and need for medically attended pulmonary care at 6-7 years of age. The estimated budget for the study is $168,400. By evaluating pulmonary function at school age, the SUPPORT – School Age Breathing Outcomes Study will not only provide valuable data on the long term pulmonary effects of SUPPORT but also provide mechanistic insights into the primary and secondary causes of pulmonary morbidity among preterm infants during childhood.

Specific Aims: The SUPPORT-School Age Breathing Outcomes Study will address 3 specific aims.
Specific Aim #1 – Measure the effect of the SUPPORT primary interventions, management with high vs. low oxygen saturation targets and early CPAP vs. prophylactic surfactant and ventilation, on pulmonary function, respiratory symptoms and need for pulmonary care among infants enrolled in the NICHD Neonatal Research Network's SUPPORT - Breathing Outcomes Trial at 6-7 years of age.

> *Hypothesis #1* - Relative to infants managed with a higher SpO2 range, infants who are managed with a lower targeted SpO2 range will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care, greater FEV_1, FEV_{25-75}, forced vital capacity (FVC) and peak flow velocities at 6-7 years of age, independent from developing BPD.
>
> *Hypothesis #2* - Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care, greater FEV_1, FEV_{25-75}, forced vital capacity (FVC) and peak flow velocities at 6-7 years of age, independent from developing BPD.

Specific Aim # 2 – Evaluate the effect of neonatal management with high vs. low oxygen saturation targets on the pulmonary response to secondary pulmonary irritants, such as environmental tobacco smoke exposure, inhaled allergens and respiratory infections during childhood by comparing pulmonary function among infants exposed to secondary respiratory irritants by SUPPORT oxygen saturation target assignment.

> *Hypothesis #3 (A Novel Second Hit Hypothesis)*- Among infants who are exposed to post-neonatal (home or outpatient) environmental respiratory irritants such as tobacco smoke, household allergens or acute viral respiratory illnesses requiring hospitalization, infants whose neonatal lung disease was managed with a lower rather than higher targeted SpO2 have less symptomatic airway dysfunction, reduced need for outpatient pulmonary care and better pulmonary function FEV_1, FEV_{25-75}, forced vital capacity (FVC) and peak flow velocities at 6-7 years of age, independent from developing BPD.

Specific Aim #3 – Evaluate the relationship between symptomatic airway dysfunction at 18-22 months of age measured by parental report as part of the Breathing Outcomes Study and respiratory symptoms, need for pulmonary care and pulmonary function at 6-7 years of age. By following individual infants from birth, through 18-22 months and on to 6-7 years of age, this aim will also evaluate how pulmonary morbidity, the pulmonary benefits of SUPPORT and the burden of pulmonary care for extremely premature infants evolves over time. This information will be valuable in developing recommendations for pulmonary follow up and care and estimating treatment costs of future extremely preterm infants.

Hypothesis #4 – BPD and symptomatic airway dysfunction at 18-22 months of age (primary outcome of the Breathing Outcomes Study) more closely predict respiratory symptoms and need for pulmonary care than abnormal pulmonary function at 6-7 years of age.

Background:

Extremely premature infants are born during a critical juncture in lung development. Perinatal environmental exposures or insults occurring during this time, such as supplemental oxygen and mechanical ventilation, interfere with normal pulmonary development resulting in impaired lung growth, structure and function. Although infants who develop BPD are at greatest risk, respiratory symptoms and need for pulmonary treatment are a significant morbidity for many preterm children. Longitudinal studies in term infants suggest that the origins of wheezing and asthma may begin in early life when genetically susceptible or environmentally sensitized infants are exposed to specific allergens, infectious agents or environmental pollutants (1;2). Premature infants, especially very low birth weight infants (VLBW, <1500 grams, approximately 32 weeks' gestation or less), commonly have respiratory exposures to concentrated oxygen and mechanical ventilation, exposures that are associated with high risk for asthma-like episodes of wheezing. How these neonatal respiratory exposures interact with common allergens, infectious agents or environmental pollutants to cause later pulmonary morbidity for premature infants is not known. Greater understanding of the interaction between neonatal and post-neonatal factors may lead to development of improved methods to avoid secondary lung injury among formerly extremely premature infants and to promote their long-term respiratory health. The potential costs are great. Because mean per capita asthma related costs may be 5 times greater for VLBW than normal weight infants, VLBW infants contribute substantially to the public health burden of wheezing in the United States (3;4) .

Absence of Long Term Pulmonary Outcome Studies of Randomized Neonatal Oxygen Exposure

There are no longitudinal pulmonary follow up studies of randomized neonatal oxygen or mechanical ventilation exposure on school age pulmonary outcome. The duration of supplemental oxygen in the neonatal period is an important predictor of pulmonary morbidity. Kennedy et al found that 20 days of oxygen had little effect on FEV1, but each additional week of supplemental oxygen after that time was associated with a progressive reduction in FEV_1 of 3% (5). However, duration of oxygen therapy does not discriminate between oxygen as a cause of lung injury and oxygen as a marker for the severity of lung injury. Whether the level of oxygen exposure in the early neonatal period affects the need for later oxygen to treat lung injury cannot be ascertained from current literature. By randomizing oxygen saturation targets and thereby level of oxygen exposure in the early neonatal period, SUPPORT is the only study with the potential to discriminate between the effect of level of concentrated oxygen as a neonatal lung toxicant and duration of supplemental oxygen as a treatment for chronic lung disease. The SUPPORT – School Age Breathing Outcomes study will provide essential information on how the level of oxygen exposure in the neonatal period affects pulmonary function.

Lack of Longitudinal Pulmonary Outcome Studies for Extremely Premature Infants

Cross sectional pulmonary outcome studies have shown that premature infants have impaired pulmonary function through childhood and into young adulthood (5-10;10;11). However, less is known about changes in pulmonary symptoms and lung function in individual patients over time. Available longitudinal pulmonary outcome studies have mostly targeted VLBW infants, a population at less risk for BPD than ELBW infants and therefore likely at less risk for ongoing pulmonary morbidity during childhood (12-14). The SUPPORT – School Age Breathing Outcomes Study will provide important longitudinal data on the natural history of pulmonary morbidity among extremely premature infants and will allow the burden of providing pulmonary care for this population to be quantified.

Neonatal Oxidant Lung Injury May Increase Susceptibility to Later, "Second Hit" Pulmonary Injury

For term infants, post-neonatal environmental exposures such as environmental tobacco smoke, household allergens and lung infections exert long-term effects on lung function. For extremely preterm infants, hyperoxia- and mechanical ventilation-associated lung injury exert long-term effects on lung structure and

function, potentially adversely affecting aging and respiratory health into adulthood. Little is known about the interplay between early neonatal respiratory exposures, such supplemental oxygen and mechanical ventilation, and later, post-neonatal environmental exposures on respiratory symptoms and lung function during childhood. Data emerging from animal and human studies suggest that neonatal exposure to concentrated oxygen not only causes direct lung injury but also alters how the lung responds to subsequent respiratory exposures such as inhaled lung irritants, allergens and infectious agents that commonly occur during childhood.

Oxygen Exposure Causes Increased Susceptibility to Respiratory Allergens

Studies in mice, rats, guinea pigs and rhesus monkeys suggest that exposure of the term or preterm lung to oxidant stress for relatively brief periods in the neonatal period is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and reactivity to subsequent environmental challenges (15-19). Schlegle exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in reduced airway number, hyperplasia of bronchial epithelium, increased mucous cells, alterations in airway smooth muscle, airway hyperreactivity, interrupted postnatal basement membrane zone differentiation and reorganization of the airway vascular and immune system. Using supplemental oxygen rather than the stronger oxidant, ozone, Schulman found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyper-reactivity at 2 and 9 days after cessation of oxygen. These studies show that exposure of infants to oxidant lung stress during early postnatal lung development sensitizes the lung, favoring increased airway reactivity, greater mucus production and development of intermittent airway obstruction associated with wheeze (20). By evaluating infants exposed to different levels of oxygen in the neonatal period and analyzing their pulmonary function by exposure to later environmental allergens or irritants (wood or tobacco smoke), the SUPPORT – School Age Breathing Outcomes Study may provide important mechanistic insights into the effects of early neonatal oxygen exposure and later reaction environmental allergens.

Neonatal Oxygen Exposure Causes Increased Susceptibility to Later Acute Respiratory Infections

Epidemiologic studies indicate children who have been exposed to concentrated oxygen in the neonatal period for treatment of RDS and/or BPD are more likely to have viral infections and out-of-school sick days than children who were not exposed to oxygen (21-23). Whereas it is well known that hyperoxia permanently disrupts postnatal lung development, less is known about how neonatal hyperoxia affects the lung's response to later exposure to respiratory pathogens and inhaled toxicants. Recently, in an animal model of hyperoxic lung injury, O'Reilly et al. showed that short-term hyperoxia at levels that are not associated with chronic alveolar changes during postnatal lung development significantly increases the sensitivity of adult mice to acute respiratory infection (24). Unlike infected siblings that developed disease and recovered, oxygen-exposed and infected mice showed enhanced recruitment of inflammatory cells into the lung leading to greater alveolar fibrosis and mortality. In unpublished data, neonatal hyperoxia resulted in significant delay in clearing influenza virus, a finding that may also contribute to greater mortality. These studies imply that neonatal hyperoxia disturbs innate immunoregulatory pathways in lung, which may contribute to the increased susceptibility to respiratory viral infections, greater disease severity and possibly reductions in lung function. By evaluating infants exposed to different levels of oxygen in the neonatal period and analyzing their pulmonary function by number of acute respiratory infections requiring hospitalization during the preschool years, the SUPPORT – School Age Breathing Outcomes Study may provide important mechanistic insights into the effects of early oxygen exposure and susceptibility to acute respiratory infections.

Alveolar Simplification Associated with BPD May Predispose Toward Earlier Lung Aging

BPD has changed over time. Whereas "old" BPD was associated with fibrosis, cystic alveolar changes and airway inflammation, "new" BPD is characterized by less airway involvement but significant alveolar simplification. Because normal lungs in healthy adults undergo emphysematous changes during aging, there is concern that premature infants who have suffered alveolar simplification as a result of BPD or extremely preterm birth will have earlier or more rapidly progressive emphysematous changes as they age. A recent study of pulmonary function among young adults (mean age 19 years) who had moderate to

severe BPD as preterm neonates found that over 80% showed signs of premature emphasematous changes (25). Hyperoxia may be a cause of alveolar simplification, in part by reducing cell proliferation and airway branching. O'Reilly has shown in laboratory animals that hyperoxia induces p-21, an inhibitor of cell proliferation that has the potential to inhibit alvelolar and airway growth (26;27). Whether management of babies with lower rather than higher saturation targets reduces oxygen exposure to the lung and thereby promotes normal lung growth prevents alveolar simplification has not been studied. The SUPPORT – Breathing Outcomes school age PFT study would measure vital capacity provide inference about lung growth and alveolarization.

Excess Respiratory Symptoms Persist Beyond Pulmonary Function Abnormalities in Preterm Infants
Preterm infants, especially those who develop BPD, are at greatest risk for persistent respiratory symptoms, need for pulmonary care and abnormal pulmonary function during childhood (12;14;23;28). In cohort studies, the prevalence of respiratory symptoms and need for pulmonary care often exceeds the prevalence of objective measurements of abnormal pulmonary function (11;14;29). In a recent study of former preterm compared with healthy term infants assessed as young adults (21 years of age), subjects born preterm had significantly more respiratory symptoms yet no difference in pulmonary function measurements of airway obstruction or reactivity (30). The SUPPORT-School Age Breathing Outcomes Study will measure both prevalence of respiratory symptoms and need for care and objective measures of pulmonary function. We hypothesize that BPD and respiratory symptoms at 18-22 months of age will be more closely predictive of ongoing respiratory symptoms and need at 6-7 years of age than of abnormal pulmonary function.

NIH Recognizes Need for Further Study of Developmental Origins of Altered Lung Physiology
In May 2008, NHLBI issued a request for applications (RFA Number: RFA-HL-08-009), entitled "Developmental Origins of Altered Lung Physiology and Immune Function". The RFA, funded through a R01 mechanism, calls for applications "that propose to perform research that will enhance the understanding of how the pre- and postnatal environments affect the interplay of the lung and immune system during development resulting in sustained changes in lung physiology and immune function that compromise respiratory health and outcomes." Although not responsive to the RO1 due to the lack of associated animal studies, the SUPPORT–School Age Breathing Outcomes Study provides a unique opportunity to study the effect of management with randomized ventilation and oxygen saturation targets on later "second hit" environmental and infectious lung injury and repair.

Summary
The SUPPORT – School Age Breathing Outcomes Study represents a unique opportunity to study the causes of short and long term pulmonary morbidity of preterm infants for several reasons, including:

- Longitudinal follow-up studies of randomized, experimental oxygen and mechanical ventilation exposure are not available and, if not performed by the NICHD Neonatal Research Network, unlikely to be performed in the future.
- By following infants exposed to randomized, experimental exposure to concentrated oxygen and mechanical ventilation through childhood, a "natural experiment" is created in which the effects of early neonatal respiratory exposures on the sensitivity or reaction to subsequent environmental exposures can be studied. Insights gained from this study may provide new insights into the mechanisms causing pulmonary morbidity among preterm infants and to create future opportunities to prevent or treat chronic respiratory disease in these infants.
- Because of its longitudinal design, valuable information will be gained on the natural history of pulmonary morbidity in preterm infants during childhood and allow the burden of treating preterm infants with respiratory to be quantified.

Methods:

Study Population:

Inclusion

- Infants enrolled in SUPPORT and Breathing Outcomes Secondary Study
- Capable of performing spirometry
- Consent for PFT

Exclusion

- Failure to gain consent for PFT

Field Work:

Tracking patients: Each NICHD NRN center will be responsible to contact eligible patients, perform pulmonary function testing and administer the Respiratory Symptom and Healthcare Utilization Questionnaire at 6-7 years of age. Yearly mailings of birthday cards with information about respiratory health of preterm infants will aid in keeping contact information of study patients up to date.

Patient incentive to participate: To facilitate recruitment and retention, a $100 honorarium will be offered to each patient choosing to participate in the SUPPORT – School Age Breathing Outcomes Study.

Outcomes:

Primary Outcome:

- Ratio of forced expiratory volume in 1 s (FEV_1) divided by that predicted based on the patients weight, height and sex

Secondary Outcomes:

- Forced vital capacity (FVC)
- Forced midexpiratory flow rate (FEV_{25-75})
- Ratio of FEV_1 to FVC (FEV%)
- Peak expiratory flow velocity (PEF)
- Prevalence of symptomatic airway dysfunction measured using a symptom questionnaire
- Use of respiratory medications in the preceding 12 months
- Need for medically attended outpatient pulmonary care (ED or office) in the preceding 12 months
- Need for respiratory related hospitalization in the preceding 12 months
- Assessment of correlation between FEV_1 and respiratory symptoms at 6-7 years of age
- Among infants with family history of asthma, to compare symptomatic airway dysfunction, need for outpatient pulmonary care and pulmonary function at 6-7 years of age by SUPPORT intervention.
- To determine the association between presence of respiratory symptoms and measured PFT abnormalities at 6-7 years of age.

Pulmonary Function Testing:

In 2007, The American Thoracic Society and European Respiratory Society issued a statement confirming that technically acceptable spirometry is possible in preschool aged children and provided guidelines on the performance and reliability of pulmonary function testing in this age group. *Pulmonary function testing for the SUPPORT – School Age Breathing Outcomes Study will be performed in accordance with the ATS / ERS statement (31).*

Spirometry is commonly performed in adults and in school age children (those aged 6–16 yr), but recent reports have confirmed that preschool children are also able to perform these maneuvers (32-39). To optimize the accuracy, reproducibility and comparability of spirometry data across centers, the SUPPORT – School Age Breathing Outcomes Study will adhere to the following ATS / ERS recommendations (31):

1. The flow–volume curve ideally should be presented to the operator in real time with the ability to also view the volume–time trace.

2. The following indices from each spirometry attempt should be available to the operator before the next attempt: FVC, FEV in *t* seconds (FEV*t*), back-extrapolated volume (VBE), and the point at which flow ceases, presented as a proportion of peak expiratory flow (PEF).
3. If it is the subject's first attempt at spirometry, a period of training is essential. The child should be familiarized with the equipment and technician.
4. Interactive computerized incentives (software used to motivate the patient) will be used to encourage the maneuver. The incentive to be used will be a volume-driven incentive or a flow- and volume-driven incentive during the time the maneuvers are to be recorded.
5. 5. Posture and noseclip use will be recorded and reported.
6. The operator should observe the child closely to ensure there is no leak, and that the maneuver is performed optimally.
7. A minimum of three maneuvers will be recorded, but no maximum number is stipulated.
8. Both volume–time and flow–volume curves should be visually inspected. The attempt should be excluded if the flow–volume curve does not demonstrate a rapid rise to peak flow, and a smooth descending limb, without evidence of cough or glottic closure.
9. If the VBE is greater than 80 ml, or 12.5% of FVC, then the curve should be reinspected, but need not necessarily be excluded.
10. If cessation of flow occurs at greater than 10% of peak flow, then this maneuver should be classified as showing premature termination. It may be possible to report timed expiratory volumes from such a maneuver, but FVC and forced expiratory flows should not be reported.
11. The highest FEV*t* and FVC should be reported, after examining data from all of the usable curves, even if they do not come from the same curve.
12. The starting point for FEV*t* should be determined by back extrapolation.
13. The method of identifying best flows should be recorded and reported. If flows are to be reported from the "best" maneuver, then this should be identified as that with the highest sum of FEV0.5 and FVC.
14. Ideally, the subject should produce at least two acceptable curves, where the second highest FVC and FEV*t* are within 0.1 L or 10% of the highest value, whichever is greater. If a single satisfactory maneuver is recorded, then these results should not be excluded simply because of poor repeatability. The number of technically satisfactory maneuvers and the repeatability results should always be reported.

Respiratory Symptom and Healthcare Utilization Questionnaire: Literature suggests that pulmonary morbidity as measured by both respiratory symptoms and pulmonary function testing persists through school age. A recent study suggests that a tendency toward greater frequency and severity of respiratory symptoms may persist beyond the age at which objective pulmonary function tests have normalized.

The respiratory symptom and healthcare utilization questionnaire to be used in this study has not yet been finalized. Several are under consideration including the Newborn Lung Project Questionnaire and modified Tucson Children's Lung Study Questionnaire. The questionnaire selected will be modified to include questions asked previously as part of the Breathing Outcomes Study. From these questions, data on the following respiratory exposures will be obtained:

Primary Exposures:
Environmental Tobacco Smoke (ETS): Presence or absence of ETS exposure will be ascertained using questions shown by Dr. Wakefield and colleagues to correlate with cotinine levels (40;41). These questions were administered as part of the Breathing Outcomes Study at 18-22 months of age and will be administered again at 6-7 years of age.

Environmental Allergens: The number of inhaled environmental allergens to which a child was exposed will be ascertained using the Breathing Outcomes Baseline Questionnaire, questions 10, 11, 12 and 13. These questions were administered as part of the Breathing Outcomes Study at 18-22 months of age and will be administered again at 6-7 years of age.

Acute Respiratory Infections: Number of acute respiratory infections receiving medical attention by 18-22 months of age will be ascertained using the Breathing Outcomes 18-22 month Questionnaire, questions # 6a, 7a or 8a of the Breathing. Additional history of the number of number of respiratory infections in the preceding 12 months will be obtained at 6-7 years of age.

Sample Size:

The Newborn Lung Project, a cohort study of VLBW infants at school age served as the basis for the assumptions used to calculate sample size. The Newborn Lung Project, a cohort study of 265 VLBW infants, studied FEV1 ratio (ratio of observed FEV1 divided by that predicted based on the patients weight, height and sex) at school age in patients with and without BPD (n - 59, FEV1 ratio - 0.78, sd - 0.13 and n - 206, FEV1 ratio - 0.88 and sd - 0.14, respectively) (14). Based on these assumptions, an effect size table was calculated (Appendix 1). In the base case (highlighted box in Appendix 1), 120 patients (60 in each SUPPORT treatment group) will be sufficient to detect an 8% difference in FEV1 with 90% power and two-sided alpha of 0.05. An 8% absolute difference in FEV1 ratio was assumed in the base case because it is both clinically significant and a conservative estimate of the expected differences between groups.

Number of Available Patients

Primary Outcome:

Based on enrollment to date, at least 750 patients will be enrolled into the SUPPORT – Breathing Outcomes Study at completion of the study. Assuming a 10% loss to follow up at 18-22 months (estimates based on current enrollment and follow up data), 25% loss to follow up at 6-7 years of age and 25% of potentially eligible patients being unable to perform testing, 384 patients are expected to be available to study (Appendix 1). Based on the 2x2 randomized design of SUPPORT, an estimated 96 patients per study intervention group (Figure 1, cells I-IV) and 192 patients per primary intervention comparison (e.g. - Figure 1, cells I & III vs. cells II & IV) will be available for study.

Fig. 1 NICHD SUPPORT Trial Design, 2 x 2 factorial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment Early CPAP	I Early CPAP + Low SpO2 (96 patients)	II Early CPAP + High SpO2 (96 patients)
Control Prophylactic/Early Surfactant	III Control + Low SpO2 (96 patients)	IV Control + High SpO2 (96 patients)

Hence, the available sample of 192 patients per primary intervention comparison (e.g. - Figure 1, cells I & III vs. cells II & IV) will be more than adequate to detect an 8% differences in FEV1 ratio through a wide range of assumptions of treatment effect (detectable difference) and standard deviation of the data (Appendix 1).

Analysis by each of 4 treatment groups: With an estimated 96 available patients per each of the 4 treatment groups defined in Figure 1, a sample size of 120 patients will be adequate to detect an 8% difference in FEV1 between each primary treatment group and allow analysis of potential synergy between combinations of treatment modalities.

Secondary Outcomes:

Subgroups of patients with or without BPD: The available study population will be adequate to allow analysis of treatment effect in important subpopulations, including comparison of the SUPPORT intervention effect among infants with and without BPD. Assuming a 35% rate of BPD among study patients, 136 infants (34 per treatment cell, Figure 2, cells I-IV) would be expected to have BPD and 248 infants would not. Again a total of 120 patients would be necessary to detect an 8% difference in FEV1 between SUPPORT Study interventions assuming 90% power,

Fig. 2 - Available Subgroup of Patients with BPD

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment Early CPAP	I Early CPAP + Low SpO2 (34 patients)	II Early CPAP + High SpO2 (34 patients)
Control Prophylactic/Early Surfactant	III Control + Low SpO2 (34 patients)	IV Control + High SpO2 (34 patients)

alpha of 0.05, and standard deviation of 12%. Based on these assumptions, the available sample of 136 patients per primary intervention comparison (e.g. - Figure 2, cells I & III vs. cells II & IV) will be more than adequate to clinically significant differences through a wide range of assumptions of treatment effect (detectable difference) and standard variation of the data (Appendix 1).

Analysis by Environmental Tobacco Smoke (ETS) Exposure: Based on assumptions above and assuming 30% of study patients will have environmental tobacco smoke (ETS) exposure, a total of 116 patients (58 per cell I & II in Figure 3) will have ETS exposure. Based on data from former VLBW infants with ETS exposure (4), a larger detectable difference between primary study intervention (high vs. low targeted saturation) is expected. The available study population will be adequate to detect 8% difference in FEV1 between high and low targeted oxygen saturation group among patients with or without ETS exposure with 80% power or a 10% difference between groups with 90% power (Appendix 1 – Sample Size Table). Evaluating the effects of ETS exposure will provide important information on whether the pulmonary benefits of SUPPORT confer resistance to secondary pulmonary irritants such as ETS exposure. Similar analyses will be performed for subgroups of infants with history of acute respiratory infections and inhaled allergen exposure during childhood.

Fig. 3 Available Subgroup of Patients exposed to ETS

	Low SpO2 85% to 89% 192 patients	High SpO2 91 to 95% 192 patients
Environmental Tobacco Smoke Exposure	I 58 Patients	II 58 Patients
No Environmental Tobacco Smoke Exposure	III 144 patients	IV 144 Patients

Analysis Plan

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample ttest, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina). Data will be presented as shown in Appendix 3. Pulmonary function tests will be reported as z-scores, in accordance with the ATS / ERS recommendations for reporting PFT results in preschool and school age children.

Budget:

In Appendix 2, a total budget of $168,400 is estimated. The budget allows for start up costs of $1,000 per center for IRB and consent preparation as well as capitated costs for patient tracking and follow up ($100 per patient), spirometry ($150 per patient), administration of the Respiratory Symptom and Healthcare Utilization Questionnaire ($50 per patient) and a participant honorarium ($100 per patient).

Appendix 1 – Estimates of Available Study Population and Necessary Sample Size

Available Patients

Estimated Available Study Population	**n**	**Remaining N**
Total Enrolled Breathing Outcomes Patients (# anticip	750	750
Loss to follow up at 18-22 months of age (10%)	75	675
Loss to follow up at 6-7 years of age (25%)	166	509
Unable to perform (25%)	125	384
Total Available Study Subjects		**384**

Available Subjects for Subroup Analysis	**Patients (N=384) With BPD (n)**	**Without BPD (n)**
35% Incidence of BPD	136	248
45% Incidence of BPD	173	211

Sample Size Table

	Detectable Difference (Absolute Value)	**High Sat Group**	**Low Sat Group**	**Sample Size (total for 2 groups) 90% Power**	**80% Power**
Primary Outcome					
Calculation using range of mean difference assumptions					
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.13)	214	160
FEV1, mean (sd)	0.08	0.80 (0.14)	0.88 (0.13)	120	90
FEV1, mean (sd)	0.10	0.78 (0.14)	0.88 (0.13)	78	58
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.10	0.78 (0.14)	0.88 (0.14)	84	62
FEV1, mean (sd)	0.10	0.78 (0.16)	0.88 (0.16)	108	82
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.08	0.80 (0.14)	0.88 (0.14)	130	98
FEV1, mean (sd)	0.08	0.80 (0.16)	0.88 (0.16)	170	126
Calculation using range of standard deviation assumptions					
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.14)	230	172
FEV1, mean (sd)	0.06	0.82 (0.14)	0.88 (0.14)	300	224

Appendix 2 - Budget

SUPPORT - School Age Breathing Outcomes Study

Proposed Budget

Start up costs	**Unit Cost**	**Total (16 Centers)**
IRB	$1,000	$16,000
Sub-total Start up Costs		**$16,000**
Capitated Costs	**Per Capita**	**Total (n=381)**
Tracking and Follow up	$100	$38,100
Spirometry	$150	$57,150
Questionnaire	$50	$19,050
Participant Honorarium	$100	$38,100
Sub-total Capitation Costs		**$152,400**
Grand Total		**$168,400**

Appendix 3 – Analysis

Outcome	Early CPAP / Low SpO2 Target	Early CPAP / High SpO2 Target	p-value	Control / Low SpO2 Target	Control / High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
Respiratory Symptoms			RR 95% CI			RR 95% CI
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

Outcome	BPD Low SpO2 Target	BPD High SpO2 Target	p-value	Without BPD Low SpO2 Target	Without BPD High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
Respiratory Symptoms			RR 95% CI			RR 95% CI
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

Outcome	ETS Exposure Low SpO2 Target	ETS Exposure High SpO2 Target	p-value	Without ETS Expsoure Low SpO2 Target	Without ETS Expsoure High SpO2 Target	p-value
Pulmonary Function Testing, mean (sd)						
Forced Expiratory Volume in 1 s (FEV1)						
Forced Vital Capacity (FVC)						
Forced Midexpiratory Flow Rate (FEV25-75)						
Ratio of FEV1 to FVC (FEV%)						
Peak Expiratory Flow Velocity (PEF)						
			RR 95% CI			RR 95% CI
Respiratory Symptoms						
Parental Report of Recurrent Wheezing (%)						
Parental Report of Chronic Cough (%)						
Pulmonary Care						
Need for Outpatient Pulmonary Medications (%)						
Need for Physician/ED Visit for Respiratory Illness (%)						
Need for Hospitalization for Respiratory Illness (%)						

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From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Monday, October 20, 2008 6:11:50 PM
Attachments: Infants with missing outcomes 10-20-08.xls

Rose,

Attached is the list of SUPPORT infants with missing outcomes this month.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
3		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
4		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
8		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.
22		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
22		The pt's follow-up window will open w/in the next month & final ROP status has not been reported. Please obtain it at the pt's Follow-up visit.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
26		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Wednesday, October 15, 2008 5:50:50 PM

Hi Rose

11 am tomorrow is the whole SUPPORT trial update, and looks like it will be about 15 minutes. I will give the MRI enrollment update as usual, but I really don't think there will be enough time for me to say anything much or anything at all about the 6-7 year follow-up issues. But I thought I would have a bit more time for update for neurodevelopmental follow-up PI's - like on Wednesday afternoon or Thursday. If there is not time this meeting, that's fine - I have too many slides anyway. I also need to get a bit more information from the Jane, the Gold Standard psychologists, and site psychologists about our concerns about the cognitive (IQ) instrument. I think it may be a good idea for me to ask a few others doing extremely preterm large cohort later follow-up (like Marlow (EPICure), Lex Doyle, Barbara Schmidt).

Let me know about the 11 am thing - I don't want to be unprepared if I will be expected to give a very very short overview of the 6-7 year follow-up progress.

Thanks

Susan
--
Susan R. Hintz, M.D., M.S. Epi
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Division of Neonatal and Developmental Medicine
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Upcoming DSMC meeting
Date: Monday, October 06, 2008 11:46:39 AM

Rose
I am OK. I hope(b) (6) .
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 06, 2008 7:45 AM
To: Finer, Neil
Subject: RE: Upcoming DSMC meeting

Neil
(b) (6)

I will give you a call tomorrow after they are done with SUPPORT.

Take care
Rose

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, October 05, 2008 10:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Upcoming DSMC meeting

I will be here Rose. Call the office and they will get me if I am not actually there – I may be in the NICU. I may be late tomorrow for the call -(b) (6) and I am just getting home.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 02, 2008 6:06 AM
To: Finer, Neil
Subject: Upcoming DSMC meeting

Neil
The DSMC meets on Tuesday October 7 to review SUPPORT. They are meeting in person at RTI here in Rockville and I will be invited over after the closed meeting. Once they state the go ahead or issues for continuation, I plan to call you. Is you office number the best one to reach you at? I would anticipate that this will be

sometime between 1-4 PM ET.
Let me know
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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From: Zaterka-Baxter, Kristin
To: gavery123@gmail.com; RJB6J@hscmail.mcc.virginia.edu; Christine A. Gleason; Willinger, Marian (NIH/NICHD) [E]; Clemons, Traci (NIH/NICHD); mikeross@ucla.edu; kant@unc.edu; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; Blaisdell, Carol (NIH/NHLBI) [E]; Keszler, Martin
Cc: meganhb@u.washington.edu; bprice@obgyn.humc.edu; Das, Abhik; Gantz, Marie; Cunningham, Meg; Huitema, Carolyn Petrie; Monica Bocaner; ekforbes@u.washington.edu; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: REMINDER: NICHD NRN Support Trial DSMC review October 7, 2008
Date: Monday, October 06, 2008 10:49:35 AM
Attachments: DSMC AGENDA20081007.pdf
Support DSMC Logistics Memo Oct 7.pdf

Dear all,

This is a reminder for tomorrows meeting; please let me know if you have any questions.

Thanks,
Kris

Kris Zaterka-Baxter
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From: Zaterka-Baxter, Kristin
Sent: Friday, September 05, 2008 4:36 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'; 'Keszler, Martin'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; Cunningham, Meg; Huitema, Carolyn Petrie; 'Monica Bocaner'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Dear all,

Please find attached the following documents for your review and information prior to the next DSMC meeting on **Tuesday October 7, 2008 in Rockville, MD (10:00am to 12:00pm EST):**

1. SUPPORT Trial Interim Report at 75% Status
2. DSMC Meeting Agenda
3. Logistics Memo
4. DSMC Roster

For those unable to attend the meeting in person or by phone, please circulate comments on the interim

report beforehand.

For those requiring hotel accommodations please contact Monica Bocaner (monica@bocaner.net) who will assist you with your reservations.

Thanks and please let me know if you have any question about the material attached.
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, August 25, 2008 4:02 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Hi all,

We would like to solidify the timeframe for the next Support Study DSMC meeting to be held in Rockville MD on October 7, 2008. We anticipate needing 2 to 3 hours for this meeting; there was only one preference for time that day and it was for morning hours. We would like to propose 10:00 am to 12:00 pm EST with lunch served afterwards (*1:00 – 3:00 pm PCT* and *3:00 – 5:00 pm UK* time for folks calling in).

Please let me know if there are any objections and please note the meeting agenda and interim report will be sent out later next week.

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Wednesday, June 18, 2008 5:22 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Hi everyone,

The next meeting for review of the Support trial interim analysis at 75% status will be held on **Tuesday October 7, 2008 at the RTI office in Rockville, MD** (Time TBD so please send preferences). The study report will be sent one month before the meeting for your review. If you can not attend the meeting, we would very much appreciate your comments/suggestions on the materials send before the meeting so that we can distribute those to the group. We will have an international, operator assisted teleconferencing system to contact folks who will join the meeting by phone. Details and the meeting agenda will be sent out with the study report.

Thanks all for your patience while were trying to find an available time to meet. Please let me know if you have any questions.
Kris

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NICHD Neonatal Research Network

Data Safety and Monitoring Committee (DSMC)

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)

The DSMC meeting to review the third interim analyses results for the *SUPPORT Trial* will be held on Tuesday October 7, 2008 in Rockville, MD (see enclosed logistics memo). The meeting will start at 10:00 AM and will finish by 12:00 PM EST.

For committee members calling in, please use the following phone number and conference code:
Dial toll free (US): 1-866-(b) (6)
Dial toll free (International): United Kingdom Dial-In #: (b) (6)

Conference code: (b) (6)

AGENDA

SESSION 1

10:00 – 10:10	Introductions	Dr. Avery
10:10 - 10:20	Presentation of the SUPPORT Trial	Dr. Das and Dr. Gantz
10:20 – 10:50	Presentation of SUPPORT Interim Monitoring Data	Dr. Das and Dr. Gantz
10:50 – 11:20	Discussion of Presentation	DSMC
11:20 – 11:50	Final Discussions and Recommendations for the SUPPORT Trial	DSMC
11:50 – 12:00	Closing Thoughts	Dr. Avery
12:00 – 1:00	Lunch	

Participants:

Gordon Avery, MD *(DSMC Chair)*	
Christine A. Gleason, MD	Marilee C. Allen, MD
Robert J. Boyle, MD	Carol J. Blaisdell, MD
Marian Willinger, PhD	Abhik Das, PhD (RTI)
Traci Clemons, PhD	Marie Gantz, PhD (RTI)
Shrikant Bangdiwala, PhD	Kris Zaterka-Baxter, RN, BSN (RTI)
Martin Keszler, MD	Carolyn Huitema, MS (RTI)
Merran A. Thomson, MD *(by phone)*	Meg Cunningham, BS (RTI)

Dr. Rosemary Higgins, NICHD Program Scientist available upon request

SUPPORT DSMC MEETING
RTI INTERNATIONAL - ROCKVILLE OFFICE
OCTOBER 7, 2008

DATE & LOCATION The meeting is scheduled for Tuesday, October 7, 2008, at RTI's Rockville office, located at 6110 Executive Blvd—9th Floor, Rockville, MD 20852.

SCHEDULE The meeting will begin Tuesday morning at 10:00 am. Breakfast and lunch will be provided. The meeting will conclude by 12:00 pm.

HOTEL Rooms will be reserved for out of town attendees at the Legacy Hotel, 1775 Rockville Pike, Rockville, MD 20852. Your reservation confirmation number will be e-mailed to you. Upon arrival you will be asked to give a credit card for incidentals, however RTI is covering the cost of your room.

Shuttle service is not provided to RTI for the meeting. We suggest attendees meet in the lobby around 9:30 am to share rides or earlier to walk the one mile to RTI.

MEALS Breakfast and lunch will be provided the day of the meeting. For out of town guests, RTI will provide reimbursement up to the allowable federal per diem for dinner on October 6 and 7. An expense form will be handed out at the meeting to cover meals, airfare and ground transportation. Please save your receipts!

TAXIS AND METRO The Legacy Hotel is located approximately forty-five minutes from Washington Reagan National Airport or Dulles International Airport. Taxis from National and Dulles Airports cost approximately $50 and from BWI, approximately $65.

Super Shuttle is available and recommend for groups traveling together. Fares are approximately $25 for the first passenger and $8 for each additional passenger. Reservations may be made online at http://www.supershuttle.com/htm/cities/dca.htm.

You may also take the Metro from Reagan National Airport to the hotel. The Legacy is located right on the Twinbrook stop on the Red Line. (13 stops from Gallery Place/Chinatown.) It is about a 45 minute ride to the DoubleTree from Gallery Place/Chinatown.

- Take the Yellow Line from the airport towards Mt. Vernon Square.
- Get off at the Gallery Place/Chinatown stop.
- Change to a Red Line train towards Shady Grove; get off at Twinbrook

SPECIAL NEEDS Any attendee with special needs (e.g. special diet, handicap access) should notify RTI Conference Coordinator Monica Bocaner at monica@bocaner.net by Tuesday, September 23. Vegetarian options will be provided at breakfast and lunch. If you have any food allergies, please let us know.

QUESTIONS For logistical information, contact RTI Conference Coordinator Monica Bocaner at monica@bocaner.net or 571-220-8756. For any other questions please contact Kris Zaterka-Baxter, NRN DCC coordinator at 919-485-7750 or kzaterka@rti.org.

If something unexpected arises that necessitates canceling your attendance at the meeting, please notify Kris Zaterka-Baxter; kzaterka@rti.org or 919-485-7750 immediately so we can cancel your hotel reservation.

From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org; Ronald N Goldberg; jeff-murray@uiowa.edu
Subject: RE: support gwas rop
Date: Wednesday, October 01, 2008 3:16:26 PM

---

ok, got it.

thanks

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/01/2008 03:15 PM

To "Michael Cotten" <cotte010@mc.duke.edu>
cc <adas@rti.org>, "Ronald N Goldberg" <goldb008@mc.duke.edu>, <jeff-murray@uiowa.edu>
Subject RE: support gwas rop

Mike
You need to have steering committee buy-in to do the project in the NRN. You can't use the NRN infrastructure without steering committee approval. The application to NHGRI will not be feasible if you do not have NRN commitment.

Rose

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, October 01, 2008 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org; Ronald N Goldberg; jeff-murray@uiowa.edu
Subject: RE: support gwas rop

I didn't anticipate getting full netwok approval so quickly that a letter would go in in Nov.....would it be prohibitive to work on a proposal to go in to nhgri and go at the same time to network?

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

10/01/2008 01:43 PM

To "Michael Cotten" <cotte010@mc.duke.edu>, "Ronald N Goldberg" <goldb008@mc.duke.edu>, <jeff-murray@uiowa.edu>
cc <adas@rti.org>
Subject RE: support gwas rop

Mike
In practical terms, it is not feasible to get through all of the needed review for a letter of support by 11/13/08 (only 6 weeks away). The Upcoming October SC meeting schedule is already tight and the deadline for concepts has past. Concepts are posted 3 weeks in advance of the SC meetings. You would also need to have the concept approved, have protocol review subcommittee meet (usually takes us 2-8 weeks to get a call set up depending on availability), then have the SC protocol presentation and a scientific vote (we usually allow 4 weeks of this so that PI's can get input from their site staff). Do you know if the RFA will be re-issued? Do you want to have a concept at the January 2009 meeting? Or will this be part of the GDB collection for genomics.

Rose

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, October 01, 2008 12:45 PM
To: Ronald N Goldberg; Higgins, Rosemary (NIH/NICHD) [E]; jeff-murray@uiowa.edu

Subject: support gwas rop

Hi Ron, Jeff and Rose,,,,

the rfa (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-08-004.html) for genomics in clinical trial dates are:

Release Date: August 19, 2008
Letters of Intent Receipt Date: October 13, 2008
Application Receipt Date: November 13, 2008

this would require a rapid presentation/rvw/generate letter. I would like to work on it from what we turned in to support at the trials' onset (advantage to look at 2 signficant disorders w/ major genetic contribution to risk, rop and bpd) in a cohort w/ the depth of covariable data on oxygen exposure that is not likely to be replicated in our lifetimes...probably 400 kids will have been seen in followup by end of 08/mid 09...leaving 800-900 kids (w/ losses due to mortality and loss to followup and failure to consent...probably 600 kids finally

because the timeline is tight, i'd like advice on first Y/N try, 2, if try...should next step be talk to Neil?

thanks

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

From: Johnson, Mary
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT event question
Date: Wednesday, October 01, 2008 10:42:47 AM
Attachments: 78031labs 9.27.08.doc
Importance: High

Hi Rose,
I've attached some labs for you. Doesn't look like anything obvious to me - but I'm not an expert either. I spoke with the clinician that was here when it happened (not available yesterday). She mentioned that the baby was doing well but looked a little grey just prior to the PICC but sats were good and he tolerated the procedure well. She had just reviewed the x-ray for line placement, saw the white out and couldn't visualize the ETT. When she went back to the room, the fellow had just extubated the baby to CPAP. The hemorrhage occurred a short while later.

Mom was relatively stable until the night of the delivery. It appears she had an acute onset of RUQ pain. All liver enzymes were markedly elevated and platelets dropped from 127 to 45 and a low of 32.

If you would like any additional information let me know.

Have a good day!

Mary

Mary E. Johnson, BSN
Research Assistant - Neonatology
313-993-7216 (O)
page (b) (6)
mejohnso@med.wayne.edu

	WBC	HGB	HCT	PLT	Comments
9/26 @ 0012	7.3	19.5	56.7	187	Marked Macrocytosis MCV – 119.4
9/26 @ 0045	3.4	17.7	51.2	195	Moderate Polychromasia MCV 119.6
9/27 @ 1650	Pulmonary Hemorrhage				
9/27 @ 1800 Post transfusion of platelets and PRBC	6.7	15.5	45.8	149	Moderate Polychromasia MCV 120.2
9/28 @ 0505	5.4	17.6	49.1	134	Slt. Anisocytosis MCV 105.4 Decreased Plt. Sufficiency
9/29 @ 0425	4.6	16.4	45.6	116	Moderate Macrocytosis MCV 104.1 Decreased Plt Sufiiciency

From: Bridge, Renee
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT
Date: Tuesday, September 23, 2008 1:54:18 PM

-----Original Message-----
From: Bridge, Renee
Sent: Tue 9/23/2008 10:51 AM
To: Rich, Wade
Subject: RE: SUPPORT

I finally got the final info on Fri. I will enter it today. Thanks for the patience

-----Original Message-----
From: Rich, Wade
Sent: Mon 9/22/2008 10:17 AM
To: Bridge, Renee
Subject: FW: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 10:17 AM
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,

We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Thanks for all the effort!!
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]; Angelita Hensman; Betty Vohr
Cc: Das, Abhik; Gantz, Marie; Dawn Andrews
Subject: RE: SUPPORT
Date: Tuesday, September 23, 2008 10:33:02 AM

Rose
See below for the best we can determine since Angelita is on vacation. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 1:00 PM
To: Abbot Laptook; Angelita Hensman; Betty Vohr
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age. We are unclear on this
14	(b) (6)	since there has been no data entered for 18 month outcome on our end as best we can tell.
CENTER	NETWORK	BPD_message
14	(b) (6)	PHY01 is expected based on NG07 but has not been entered Data has been entered on 9/23
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed Lost to f/u (NF12) entered 9/19
14	[redacted]	FU window has closed but NF05 and NF09a have not been completed Lost to f/u (NF12) entered 9/19

Thank you for your continued outstanding job in this trial. Your recruitment has been spectacular!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Monica Konstantino
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; Rich
Subject: Re: Support baby
Date: Monday, September 22, 2008 3:59:16 PM

Zaterka-Baxter, Kristin wrote:

> Hi Monica,
> I talked to Rose this morning about your Support baby; could you please send me the network ID so we can note it here.
> Thanks,
> Kris
>
> *Kris Zaterka-Baxter*
> *RTI International*
> *3040 Cornwallis Road*
> *P.O. Box 12194*
> *RTP, NC 27709-2194 USA*
> *(tel) 919-485-7750*
> *(fax) 919.485.7762*
> *kzaterka@rti.org*
> *www.rti.org*
>
> *Federal Express/UPS/DHL Shipping Address:*
> *Kris Zaterka-Baxter*
> *RTI International*
> *3040 Cornwallis Road*
> *RTP, NC 27709 USA*

Hi Kris, I just faxed you and Rose the MedWatch form for that baby. His network ID is (b) (6) 1. We ended up putting the baby on the study oximeter this morning after talking to the attending caring for the baby and his parents. The surfactant ommission and the failure to place the oximeter on the baby within 2 hours we treated as a protocol deviation and I have filled out the appropriate forms. thanks and let me know if you need any more info,
Monica

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ira Adams-Chapman
Subject: Re: SUPPORT
Date: Monday, September 22, 2008 3:41:29 PM

Rose,
These are some hard ones. Still workin on 2 of them.
Ellen

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Hi

We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP message	
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye	Still trying to get in touch with this mother. She does not have a phone and the grandmother cannot reach her either.

CENTER	NETWORK	EU message	
9	(b) (6)	EU window has closed but NE05 and NE09a have not been completed	This child is lost to follow-up. Entered in computer.
9		EU window has closed but NE05 and NE09a have not been completed	This trying to arrange home visit--child in foster care in (b) (6)

Thanks for all the effort!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Program Officer, Pediatrics Branch
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higginsr@mail.nih.gov

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B; Hamer, Faithe Angeline; Dusick, Anna M.
Subject: RE: SUPPORT
Date: Monday, September 22, 2008 3:15:19 PM

Hi Rose (b) (6) will be in the transmission tomorrow.
(b) (6) has RHC'd and passed away (b) (6) His window did not open up until 4/24/08 so pt was never seen for a f/u visit. NF12 had been entered.

leslie

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (6) (pager)

From: Dusick, Anna M.
Sent: Monday, September 22, 2008 2:49 PM
To: Wilson, Leslie Dawn
Cc: Poindexter, Brenda B
Subject: RE: SUPPORT

Is the (b) (6) someone we know?

From: Poindexter, Brenda B
Sent: Monday, September 22, 2008 12:55 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Wilson, Leslie Dawn; Dusick, Anna M.
Cc: Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT

Rose,
We'll get back to you right away. Please delete Leslie Richard from your distribution lists – she is no longer working at IU.
Thanks, Brenda

Brenda Poindexter, MD, MS
Associate Professor of Clinical Pediatrics
Section of Neonatal-Perinatal Medicine
Riley Hospital for Children
Indianapolis, IN
(317) 274-4768

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 12:54 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn; Richard, Leslie Doreen; Dusick, Anna M.
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
12	(b) (6)	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
CENTER	NETWORK	FU_message
12	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Thanks for all the effort!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, September 22, 2008 2:36:17 PM

Rose
Per our conversation this AM, Neil feels that the kid should remain in the trial, and that deviations should be documented.
Wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 10:17 AM
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
22	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Thanks for all the effort!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Monday, September 22, 2008 2:05:48 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> HI,
> We are missing a few SUPPORT outcomes. Can you let us know how you are doing?
>
CENTER	NETWORK	BPD_message
13	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

> Thanks for all the effort
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
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> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Hi Rose, that baby is still here and when he gets discharged, possibly this week, then we will go ahead and enter the completed generic chart, thanks.
Monica

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; "Michelle Walsh"; "nancy newman"
Cc: "Gantz, Marie"; "Das, Abhik"
Subject: RE: SUPPORT outcomes
Date: Monday, September 22, 2008 1:48:44 PM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 12:37 PM
To: Michelle Walsh; nancy newman; Bonnie Siner
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT outcomes

HI,
We are missing a few SUPPORT outcomes. I realize that you had not computer for some length of time for transmission. This is outstanding given your excellent recruitment into this trial. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.-ALREADY ENTERED.

CENTER	NETWORK	FU_message
3	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed-BAYLEY HAD TO BE RESCHEDULED FOR THIS WEEK.

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

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT missing outcomes
Date: Monday, September 22, 2008 1:13:33 PM

I think you are correct, however, Miami might have accidentally miscoded two of their ROP cases. The error messages they have for these two is "Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status." I suspect that they intended to code these as 'Final ROP status determined at 18M FU'=N instead of Y. If they had answered the question with "No" they would not have received a missing outcomes message.

Marie

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 22, 2008 12:49 PM
To: Gantz, Marie
Subject: RE: SUPPORT missing outcomes

Marie
There are some on here for Miami, but I was under the impression they had sent everything they had, correct?
Let me know

Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, September 22, 2008 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

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

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kennedy, Kathleen A"; "Tyson, Jon E"; "Mcdavid, Georgia E"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: SUPPORT
Date: Monday, September 22, 2008 1:12:50 PM

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

	NETWORK	ROP_message
18	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
18	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
18	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
18	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
18	(b) (6)	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)1	The patient is within their Fol-up window and final ROP status has not been reported.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
18	(b) (6)	Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing
CENTER	NETWORK	FU_message
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
18	(b) (6)	FU window has closed but NF09a has not been completed

Thanks for all the effort!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Abbot Laptook"; "Angelita Hensman"; "Betty Vohr"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: SUPPORT
Date: Monday, September 22, 2008 12:59:59 PM

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
14	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
CENTER	NETWORK	BPD_message
14	(b) (6)	PHY01 is expected based on NG07 but has not been entered
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Thank you for your continued outstanding job in this trial. Your recruitment has been spectacular!!!
Rose

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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "richard.ehrenkranz@yale.edu"; "monica.konstantino@yale.edu"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: SUPPORT
Date: Monday, September 22, 2008 12:56:42 PM

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	BPD_message
13	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

Thanks for all the effort
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Monday, September 22, 2008 12:53:19 PM

Baby just arrived back in states was lost in Mexico and we did him on Thursday will get info in asap.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 9/22/2008 11:39 AM >>>
HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	FU_message
4	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Seetha Shankaran"; "Sood, Beena"; "Becky bara"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: SUPPORT
Date: Monday, September 22, 2008 12:47:58 PM

HI,
We are missing a few SUPPORT outcomes. Can you let us know how you are doing?

CENTER	NETWORK	ROP_message
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
5	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 has not been completed

Thanks for all the effort!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Monday, September 22, 2008 12:12:31 PM
Attachments: Infants with missing outcomes 09-19-08.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
8		Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
14		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient's follow-up window has closed and final ROP status has not been reported.
19		The patient is within their Fol-up window and final ROP status has not been reported.
19		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Duara, Shahnaz
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete
Date: Tuesday, September 16, 2008 4:29:24 PM

I need to speak to the authors in a conference call to see if there is any interest in pursuing this. Could you set up something for Sept 29 or 30?

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, September 16, 2008 4:28 PM
To: Duara, Shahnaz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete

We also need an update on whether you plan on rewriting Dr. Navarrete's paper:

Navarrete C; Saha S, Das A; Fanaroff AA; Goldberg RN; Higgins RD; Oh W; Stoll BJ; Duara S for the NICHD Neonatal Research Network Risks and Benefits of Prophylactic Indomethacin in Extremely Low Birth Weight Infants: Does Post-Menstrual Age Make a Difference? 6/5/08
Navarrete: I have been trying to get around reviewers' comments...What they were asking were impossible to accomplish. Seems unacceptable for the reviewers for any kind of publication.

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, July 16, 2008 9:53 AM
To: 'Duara, Shahnaz'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete

Hi again Shahnaz,

As mentioned on my previous email about your pending papers, the NRN Steering Committee will be meeting next week. The Publications Subcommittee needs to present updates on all pending publications.

You had previously wanted to consider whether one of the other coauthors would be interested in writing up Christina Navarrete's results for the manuscript listed below. Can you please let me know what your decision is on this?

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

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Thursday, June 19, 2008 11:04 AM
To: 'Duara, Shahnaz'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete

Hi Shahnaz,

For the Publications tracker, should I list this paper as still pending or as withdrawn? If someone else is going to take the lead on writing it, please let me know so that I can update the information.

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

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, June 05, 2008 3:09 PM
To: 'Duara, Shahnaz'
Subject: RE: Publications | Navarrete

I would discuss with the co-authors and make a decision.
Regards
Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Thursday, June 05, 2008 2:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Publications | Navarrete

Rose,

I am very sorry to see that Tina is frustrated to the extreme by the review we got back from John Tyson and wishes to withdraw the paper. Is

this your read as to the best course of action? I was too angry for a while to deal with it, but I think it is a lot of wasted work. Do you agree that the paper should be abandoned?

Shahnaz

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thursday, June 05, 2008 1:49 PM
To: Navarrete, Cristina
Cc: sduara@miami.edu
Subject: RE: Publications | Navarrete

OK. With Shahnaz's concurrence, I will mark this as Withdrawn then.

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Thursday, June 05, 2008 1:30 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete

Hello Stephanie!
I have been all this time trying to get around the comments of the reviewers, however it has been futile. What they were asking were impossible to accomplish. I regret to say that the manuscript seems to be unacceptable for the reviewers for any kind of publication.

Cristina T. Navarrete, MD
Assistant Professor of Clinical Pediatrics
Division of Neonatology
305-585-6408

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thu 6/5/2008 12:54 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Navarrete, Cristina
Cc: sduara@miami.edu
Subject: RE: Publications | Navarrete

Hi Cristina,

I'm updating the NRN publications tracker for the upcoming Steering Committee meeting. I'm asking for updates for any items that I have not heard about in 6 months or longer.

Can you please send me a quick status update on:

Authors

Paper Working Title

Comments/Status

Last
Update

Navarrete C; Saha S, Das A; Fanaroff AA; Goldberg RN; Higgins RD; Oh W; Stoll BJ; Duara S for the NICHD Neonatal Research Network

Risks and Benefits of Prophylactic Indomethacin in Extremely Low Birth Weight Infants: Does Post-Menstrual Age Make a Difference?

4/2007 Sent to Dr Duara for revision;
8/9/07 Revised version received

9/26/2007

Please note that any items that we have not gotten an update on in over a year will be marked as Withdrawn on the tracker.

Thank you,

Stephanie

Stephanie Wilson Archer

The Eunice Kennedy Shriver

National Institute of Child Health and Human Development

Pregnancy & Perinatology Branch

6100 Executive Boulevard, Room 4B03

Rockville, MD 20852

Tel. 301-496-0430

Fax 301-496-3790

archerst@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, March 26, 2008 10:39 AM
To: Archer, Stephanie (NIH/NICHD) [E]; 'CNavarrete@med.miami.edu'
Cc: 'sduara@miami.edu'
Subject: RE: Publications | Navarrete

Hi Cristina,

Just a reminder that I still need an update on your manuscript.

Thanks,

Stephanie

Stephanie Wilson Archer

The Eunice Kennedy Shriver

National Institute of Child Health and Human Development

Pregnancy & Perinatology Branch

6100 Executive Boulevard, Room 4B03

Rockville, MD 20852

Tel. 301-496-0430

Fax 301-496-3790

archerst@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Friday, March 14, 2008 11:59 AM
To: 'CNavarrete@med.miami.edu'
Cc: 'sduara@miami.edu'
Subject: Publications | Navarrete

Hi Cristina,

It's that time again... I need to get updates on pending NRN publications for the upcoming Steering Committee meeting.

Can you please send me a quick status update on:

* Risks and Benefits of Prophylactic Indomethacin in Extremely Low Birth Weight Infants: Does Post-Menstrual Age Make a Difference? (Last update: 8/9/07 Revised version received)

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: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT update for subcommittee meeting 9/12
Date: Friday, September 12, 2008 11:29:26 AM

Hi Rose: I am leaving for the Med school: if able I will
Call in at 1pm by cell phone, but am not sure where we
Will be in our teaching at that time.
I am supportive of the secondary study to go forward.

Michele Walsh
beeper(b) (6)
Ph 216 844 5109

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 12, 2008 11:06 AM
To: Finer, Neil; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: SUPPORT update for subcommittee meeting 9/12

We will also discuss this secondary on the call today at 1 PM ET

866-675-(b) (6)with passcode(b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 05, 2008 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject: FW: SUPPORT update for subcommittee meeting 9/12

Hello Everyone
Here is an agenda for next weeks meeting, and the updates from Marie (Thanks Marie)

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations - Currently 1158 per Sept, > 87% of total, projected completion by Feb 2009.

2. Review status of Secondaries-
   MRI
   Breathing Outcomes
   Nutrition
   Antenatal consent

3. Other Issues

Many thanks for the great work by everyone!!

Please let me know if there are additional issues you would like added to the agenda
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

Visit us at www.UHhospitals.org.

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: SUPPORT update for subcommittee meeting 9/12
Date: Friday, September 12, 2008 11:17:13 AM

Rose and Neil:

I have been concerned of slowing of enrolment. It is something we may want to discuss. Despite more sites, our enrolment has decreased to ~ the lowest levels ever.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 12, 2008 10:06 AM
To: Finer, Neil; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
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Neil N. Finer, M.D.
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT update for subcommittee meeting 9/12
Date: Friday, September 12, 2008 10:47:23 AM

Yes, our analyses always adjust for this dependence.

Abhik Das
Senior Research Statistician
RTI International

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 12, 2008 10:39 AM Eastern Standard Time
To: Das, Abhik
Subject: FW: SUPPORT update for subcommittee meeting 9/12

I think you looked into the twin issue, right?

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Thursday, September 11, 2008 5:30 PM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT update for subcommittee meeting 9/12

Neil and Rose: I will be teaching at the Medical School during

The call time slot. I will review the attachments and let you know if

Anything catches my eye. How can we speed up these final

Enrollments? Also: see lead article in this months Pediatrics

On the genetic contribution to BPD, and assessment of trial outcomes

In multiples. I don't recall how we handled enrollment of twins- were they randomized

Separately? The paper on multiples from the NOCLD paper has been accepted, which

Indicates a need to take into account the non-independent nature of the twins-

We will need to address, and perhaps now is a good time to think this through?

Michele Walsh

beeper(b) (6)

Ph 216 844 5109

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 05, 2008 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
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Neil

Neil N. Finer, M.D.

Professor of Pediatrics

Director, Division of Neonatal-Perinatal Medicine

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Facsimile: 619.543.3812

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From: Susan Hintz
To: neil finer
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT neuroimaging numbers for call 9/12
Date: Wednesday, September 10, 2008 4:19:03 PM
Attachments: Sept2008SUPPORTNeuroUpdateHINTZ.doc

Hi Neil and Rose,

Neil, as I mentioned to Rose (b) (6) (b) (6) (b) (6) Rose told me she would present my (brief) numbers update on the Neuroimaging and Neurodevelopmental Outcome secondary during the SUPPORT conference call. I hope that is OK with you.

Attached is the update. I am very excited and encouraged by the number of MRI's that we have already, and I think both the 18-22 month and 6-7 year follow-up projects will be incredibly exciting.

By way of an update for you Neil, we have been having vigorous and frequent communications among several of the members of 6-7 year extended follow-up subcommittee to finalize some of the remaining issues re: best instruments/tests for the 6-7 year visit. The majority of discussion has been around identifying an appropriate Spanish language alternative for the WPPSI - we are making progress.

Let me know if you have questions

Susan

--
Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351

Enrollment/Process update

- 15 sites enrolling; data through 8/31/08
  - **517 patients** have been enrolled in the SUPPORT Neuroimaging secondary
    - **~394 patients** have completed successful 35-42 week *MRI*
      - **Of the 123 patients enrolled who do not have MRI:**
        - 78 patients died before MRI
        - 21 with MRI01 not yet complete or window for MRI not reached
        - 24 with other issues including technical/availability (4), attempted but movement or uncooperative (5), patient discharged or transferred prior to MRI (4), clinically unstable (3), other (8)

Tracking enrollment

- THANK YOU to all the coordinators who continue to key the first part of the MRI01 form as soon as they can – this has allowed us to keep our tracking as up to date as possible.

Please call or email with questions, comments, and suggestions

Susan Hintz
650-723-5711 (office)
Email: srhintz@stanford.edu

THANKS TO ALL THE SITES FOR THE HARD WORK ON THIS STUDY!

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN Support Trial DSMC review October 7, 2008
Date: Wednesday, September 10, 2008 9:03:32 AM
Attachments: DSMC AGENDA20081007.pdf
Support DSMC Logistics Memo Oct 7.pdf
DSMC Roster20080828.pdf

Hi,
Just wanted to give you this info for time and logistics (I deleted the interim report). We are planning for lunch at noon after the meeting and can call you for the wrap up at the end of the meeting or if the committee has any questions beforehand. We also plan to have a cake for Dr. Avery and present him with the letter or book Carolyn is putting together on behalf of the network.
Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Friday, September 05, 2008 4:36 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'; 'Keszler, Martin'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; Cunningham, Meg; Huitema, Carolyn Petrie; 'Monica Bocaner'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Dear all,

Please find attached the following documents for your review and information prior to the next DSMC meeting on **Tuesday October 7, 2008 in Rockville, MD (10:00am to 12:00pm EST):**

1. SUPPORT Trial Interim Report at 75% Status
2. DSMC Meeting Agenda
3. Logistics Memo
4. DSMC Roster

For those unable to attend the meeting in person or by phone, please circulate comments on the interim report beforehand.

For those requiring hotel accommodations please contact Monica Bocaner (monica@bocaner.net) who will assist you with your reservations.

Thanks and please let me know if you have any question about the material attached.
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, August 25, 2008 4:02 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Hi all,

We would like to solidify the timeframe for the next Support Study DSMC meeting to be held in Rockville MD on October 7, 2008. We anticipate needing 2 to 3 hours for this meeting; there was only one preference for time that day and it was for morning hours. We would like to propose 10:00 am to 12:00 pm EST with lunch served afterwards (*1:00 – 3:00 pm PCT* and *3:00 – 5:00 pm UK* time for folks calling in).

Please let me know if there are any objections and please note the meeting agenda and interim report will be sent out later next week.

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Wednesday, June 18, 2008 5:22 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Hi everyone,

The next meeting for review of the Support trial interim analysis at 75% status will be held on **Tuesday October 7, 2008 at the RTI office in Rockville, MD** (Time TBD so please send preferences). The study report will be sent one month before the meeting for your review. If you can not attend the meeting, we would very much appreciate your comments/suggestions on the materials send before the meeting so that we can distribute those to the group. We will have an international, operator assisted teleconferencing system to contact folks who will join the meeting by phone. Details and the meeting agenda will be sent out with the study report.

Thanks all for your patience while were trying to find an available time to meet. Please let me know if you have any questions.
Kris

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NICHD Neonatal Research Network

Data Safety and Monitoring Committee (DSMC)

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)

The DSMC meeting to review the third interim analyses results for the *SUPPORT Trial* will be held on Tuesday October 7, 2008 in Rockville, MD (see enclosed logistics memo). The meeting will start at 10:00 AM and will finish by 12:00 PM EST.

For committee members calling in, please use the following phone number and conference code:
Dial toll free (US): 1-866-674(b) (6)
Dial toll free (International): United Kingdom Dial-In #: (b) (6)

Conference code: (b) (6)

AGENDA

SESSION 1

10:00 – 10:10	Introductions	Dr. Avery
10:10 - 10:20	Presentation of the SUPPORT Trial	Dr. Das and Dr. Gantz
10:20 – 10:50	Presentation of SUPPORT Interim Monitoring Data	Dr. Das and Dr. Gantz
10:50 – 11:20	Discussion of Presentation	DSMC
11:20 – 11:50	Final Discussions and Recommendations for the SUPPORT Trial	DSMC
11:50 – 12:00	Closing Thoughts	Dr. Avery
12:00 – 1:00	Lunch	

Participants:

Gordon Avery, MD *(DSMC Chair)*	
Christine A. Gleason, MD	Marilee C. Allen, MD
Robert J. Boyle, MD	Carol J. Blaisdell, MD
Marian Willinger, PhD	Abhik Das, PhD (RTI)
Traci Clemons, PhD	Marie Gantz, PhD (RTI)
Shrikant Bangdiwala, PhD	Kris Zaterka-Baxter, RN, BSN (RTI)
Martin Keszler, MD	Carolyn Huitema, MS (RTI)
Merran A. Thomson, MD *(by phone)*	Meg Cunningham, BS (RTI)

Dr. Rosemary Higgins, NICHD Program Scientist available upon request

SUPPORT DSMC MEETING
RTI INTERNATIONAL - ROCKVILLE OFFICE
OCTOBER 7, 2008

DATE & LOCATION The meeting is scheduled for Tuesday, October 7, 2008, at RTI's Rockville office, located at 6110 Executive Blvd—9th Floor, Rockville, MD 20852.

SCHEDULE The meeting will begin Tuesday morning at 10:00 am. Breakfast and lunch will be provided. The meeting will conclude by 12:00 pm.

HOTEL Rooms will be reserved for out of town attendees at the Legacy Hotel, 1775 Rockville Pike, Rockville, MD 20852. Your reservation confirmation number will be e-mailed to you. Upon arrival you will be asked to give a credit card for incidentals, however RTI is covering the cost of your room.

Shuttle service is not provided to RTI for the meeting. We suggest attendees meet in the lobby around 9:30 am to share rides or earlier to walk the one mile to RTI.

MEALS Breakfast and lunch will be provided the day of the meeting. For out of town guests, RTI will provide reimbursement up to the allowable federal per diem for dinner on October 6 and 7. An expense form will be handed out at the meeting to cover meals, airfare and ground transportation. Please save your receipts!

TAXIS AND METRO The Legacy Hotel is located approximately forty-five minutes from Washington Reagan National Airport or Dulles International Airport. Taxis from National and Dulles Airports cost approximately $50 and from BWI, approximately $65.

Super Shuttle is available and recommend for groups traveling together. Fares are approximately $25 for the first passenger and $8 for each additional passenger. Reservations may be made online at http://www.supershuttle.com/htm/cities/dca.htm.

You may also take the Metro from Reagan National Airport to the hotel. The Legacy is located right on the Twinbrook stop on the Red Line. (13 stops from Gallery Place/Chinatown.) It is about a 45 minute ride to the DoubleTree from Gallery Place/Chinatown.

- Take the Yellow Line from the airport towards Mt. Vernon Square.
- Get off at the Gallery Place/Chinatown stop.
- Change to a Red Line train towards Shady Grove; get off at Twinbrook

SPECIAL NEEDS Any attendee with special needs (e.g. special diet, handicap access) should notify RTI Conference Coordinator Monica Bocaner at monica@bocaner.net by Tuesday, September 23. Vegetarian options will be provided at breakfast and lunch. If you have any food allergies, please let us know.

QUESTIONS For logistical information, contact RTI Conference Coordinator Monica Bocaner at monica@bocaner.net or 571-220-8756. For any other questions please contact Kris Zaterka-Baxter, NRN DCC coordinator at 919-485-7750 or kzaterka@rti.org.

If something unexpected arises that necessitates canceling your attendance at the meeting, please notify Kris Zaterka-Baxter; kzaterka@rti.org or 919-485-7750 immediately so we can cancel your hotel reservation.

NICHD Neonatal Research Network DSMC Membership Roster 08/28/08

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NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

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blaisdellcj@nhlbi.nih.gov

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT call?
Date: Monday, September 08, 2008 11:50:01 AM

Hi Rose

Is the SUPPORT conference call for September 12th supposed to be the equivalent of the SUPPORT subcommittee meet for a Network meeting? If so, I guess I better put together my SUPPORT secondary update (i.e., # enrolled, etc). What else will be discussed on that call?? Am I supposed to give an update about 6-7 year follow-up issues, etc? I would guess not, but I want to make sure I know what I am supposed to have ready to talk about -

Honestly, I wasn't sure that I was even supposed to join that call - (b) (6) [redacted] but we can rearrange to another date.

Let me know

Susan

From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	FW: SUPPORT update for subcommittee meeting 9/12
Date:	Friday, September 05, 2008 4:36:12 PM
Attachments:	SUPPORT Enrollment 9-02-08.doc SUPPORT Adverse Events 09-02-08.doc SUPPORT Use of HFNC 09-02-08.doc SUPPORT Protocol Deviations - old vs new 09-02-08.doc SUPPORT Protocol Deviations by center - old vs new 09-02-08.doc All Centers pct in range through Aug08.rtf

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Hello Everyone
Here is an agenda for next weeks meeting, and the updates from Marie (Thanks Marie)

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations - Currently 1158 per Sept, > 87% of total, projected completion by Feb 2009.

2. Review status of Secondaries-
   MRI
   Breathing Outcomes
   Nutrition
   Antenatal consent

3. Other Issues

Many thanks for the great work by everyone!!

Please let me know if there are additional issues you would like added to the agenda
Neil

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SUPPORT Enrollment as of September 2, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	1158	88%

Enrollment by Center

Center	<Mar-08	Mar-08	Apr-08	May-08	Jun-08	Jul-08	Aug-08	Total
3	84	4	1	1	5	2	0	97
4	47	7	4	2	1	2	2	65
5	44	4	2	2	4	1	4	61
8	17	0	0	0	0	0	0	17
9	60	3	5	0	4	1	5	78
11	72	4	2	4	0	1	0	83
12	57	1	1	0	1	2	1	63
13	25	0	1	0	2	3	1	32
14	90	6	6	5	3	0	0	110
15	35	3	1	2	0	3	2	46
16	135	8	7	5	4	7	2	168
18	63	2	2	2	4	1	0	74
19	52	1	0	0	1	1	0	55
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	57	1	1	1	0	1	1	62
23	41	1	0	0	3	0	0	45
24	20	0	1	3	0	1	0	25
25	30	4	5	6	0	0	0	45
26	11	1	0	0	2	1	0	15
Total	957	50	39	33	34	27	18	1158
Centers		17	17	17	17	17	17	
Avg/center		2.9	2.3	1.9	2.0	1.6	1.1	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	4.5
2.5	3.6
3	3.0

Percent of SUPPORT infants with selected adverse events as of September 2, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.5	9.3	4.3
Air leak (pneumothorax, PIE, pneumopericardium)	9.5	12.5	7.3
Pulmonary hemorrhage	6.8	10.7	3.8
Severe IVH (grades III-IV)	14.2	20.4	9.7

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak (pneumothorax)	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of September 2, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			4	5%
4			10	18%
5			9	15%
9			12	18%
11	1	5%	6	9%
12			9	17%
13			5	16%
14	1	5%	6	7%
15			1	2%
16			3	2%
18	1	5%	7	13%
19			9	23%
22			1	5%
23			1	2%
24			1	4%
25			7	16%
Total	3	1%	91	10%

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – September 2, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	3
Surfactant not given in the first hour (surfactant group)	28
Surfactant not given in the first hour (CPAP group)	32
Oximeter not started within 2 hours	24
Infant received incorrect treatment assignment	15
Failure to use study oximeter at times required by protocol	71
Non-study (unmasked) oximeter used at same time as study oximeter	8
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate CPAP infant if all criteria met	4
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	23
Randomization/consent errors	24
Other	6
Total	260

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	87
Infant received incorrect treatment assignment	15
Failure to use study oximeter at times required by protocol	71
Non-study (unmasked) oximeter used at same time as study oximeter	8
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	8
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate infant if all criteria met	5
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	23
Randomization/consent errors	24
Other	6
Total	260

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	0
Surfactant not given in the first hour (surfactant group)	7
Surfactant not given in the first hour (CPAP group)	7
Oximeter not started within 2 hours	7
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	21
Infant received incorrect treatment assignment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – September 2, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			1								1	1									3
Surfactant not given in the first hour (surfactant group)	2	4	2			3	1	2	2		3		1					5	3		28
Surfactant not given in the first hour (CPAP group)	3	2				2		1	6	3	4	1	1				1	5	2	1	32
Oximeter not started within 2 hours	1	1	2		1	1	2			2	2	2	2			1	2	1	4		24
Infant received incorrect treatment assignment	3		1			1	1			2	4		1				1		1		15
Failure to use study oximeter at times required by protocol	2	4	15		2	5	5	1	9		7		2				3	5	8	3	71
Non-study (unmasked) oximeter used at same time as study ox						2	1			1			1						3		8
Mechanical ventilation initiated for other than study criteria																	1		1		2
NSIMV initiated in infant not previously intubated	1				1			1			5										8
Extubation (excluding unplanned) for other than study criteria						2			5		2										9
Failure to extubate CPAP infant if all criteria met								1		3											4
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1										2
Infant received postnatal steroids in first 21 days of life	1					2		2	5		3	8	1				1				23
Randomization/consent errors	1	1	4		3	1				3		4	2			1	4				24
Other									1	1	2								2		6
Total	14	12	26	0	7	20	10	8	28	15	34	16	11	0	0	2	13	16	24	4	260

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – September 2, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2%								1%	2%									0%
Surfactant not given in the first hour (surfactant group)	3%	7%	3%			5%	2%	6%	2%		2%		3%					20%	7%		3%
Surfactant not given in the first hour (CPAP group)	4%	4%				3%		3%	7%	7%	3%	2%	3%				2%	20%	4%	7%	4%
Oximeter not started within 2 hours	1%	2%	3%		2%	2%	4%			5%	2%	4%	5%			5%	4%	4%	9%		3%
Infant received incorrect treatment assignment	4%		2%			2%	2%			5%	3%		3%				2%		2%		2%
Failure to use study oximeter at times required by protocol	3%	7%	25%		3%	8%	9%	3%	10%		5%		5%				7%	20%	18%	20%	8%
Non-study (unmasked) oximeter used at same time as study ox						3%	2%			2%			3%						7%		1%
Mechanical ventilation initiated for other than study criteria																	2%		2%		0%
NSIMV initiated in infant not previously intubated	1%				2%			3%			4%										1%
Extubation (excluding unplanned) for other than study criteria						3%			6%		2%										1%
Failure to extubate CPAP infant if all criteria met								3%		7%											0%
Failure to extubate surfactant infant if all criteria met						2%															0%
Infant intubated without meeting study criteria			2%								1%										0%
Infant received postnatal steroids in first 21 days of life	1%					3%		6%	6%		2%	15%	3%				2%				3%
Randomization/consent errors	1%	2%	7%		5%	2%				7%		7%	5%			5%	9%				3%
Other									1%	2%	2%								4%		1%
Total protocol deviations	19%	22%	43%		11%	31%	19%	26%	32%	34%	26%	29%	28%		0%	10%	29%	64%	53%	27%	29%
Total number of infants enrolled	73	55	61	0	65	64	53	31	88	44	130	55	40	0	1	21	45	25	45	15	911

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0
Surfactant not given in the first hour (surfactant group)	2			1		2	1				1										7
Surfactant not given in the first hour (CPAP group)	4			2												1					7
Oximeter not started within 2 hours						1					5	1									7
Infant received incorrect treatment assignment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox.															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors														2							2
Other						1					1										2
Total	9	4	0	4	0	7	1	0	4	0	16	2	1	3	3	8	0	0	0	0	62

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0%
Surfactant not given in the first hour (surfactant group)	8%			6%		11%	10%				3%										3%
Surfactant not given in the first hour (CPAP group)	17%			12%												2%					3%
Oximeter not started within 2 hours						5%					13%	5%									3%
Infant received incorrect treatment assignment	4%			6%							11%					2%					3%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						6%
Non-study (unmasked) oximeter used at same time as study ox															14%						0%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	38%	40%		24%	0%	37%	10%	0%	18%	0%	42%	11%	7%	33%	43%	20%					25%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations collected on other forms.

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Apr08-Aug08	Days of life 1-14	All centers	11798	36.1	9.4	77.3	13.2
		Center 3	951	28.9	9.0	75.0	16.0
		Center 5	1662	28.1	11.4	67.2	21.4
		Center 9 site A	718	48.8	9.4	83.1	7.5
		Center 11	881	16.9	8.8	65.7	25.6
		Center 14	863	37.6	7.3	82.9	9.9
		Center 16	1786	40.3	9.0	81.6	9.3
		Center 18	680	29.0	6.2	72.7	21.1
		Center 25	1116	53.1	6.0	85.4	8.6
	Day 15 to 36 wks	All centers	51964	30.6	12.6	69.0	18.4
		Center 3	2628	31.1	16.3	67.6	16.2
		Center 4	2286	30.7	10.6	73.3	16.0
		Center 5	4458	24.9	9.9	64.5	25.6
		Center 9 site A	5473	33.5	13.5	71.2	15.3
		Center 11	2968	17.3	9.0	56.7	34.3
		Center 14	6557	36.0	9.0	70.9	20.1
		Center 15	3818	29.5	17.5	72.5	10.0
		Center 16	7742	33.6	12.0	75.5	12.5
		Center 24	2597	22.0	22.1	58.6	19.2
		Center 25	9069	35.8	10.3	69.0	20.7
Jan08-Mar08	Days of life 1-14	All centers	8682	35.4	9.6	78.4	12.0
		Center 3	952	35.7	9.9	77.3	12.9
		Center 5	829	23.5	7.7	66.4	25.9
		Center 11	901	24.7	10.2	76.9	13.0
		Center 14	591	51.6	4.7	83.5	11.7
		Center 16	1499	37.7	10.9	83.0	6.1
		Center 25	889	54.7	4.1	85.4	10.4
	Day 15 to 36 wks	All centers	34499	27.4	14.2	67.0	18.8
		Center 3	3701	22.1	21.3	65.8	12.8
		Center 5	3691	28.3	11.8	66.1	22.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 11	2549	16.4	8.3	60.6	31.1
		Center 12	3242	37.3	11.0	68.5	20.5
		Center 14	1807	29.9	11.5	69.3	19.3
		Center 16	6857	29.1	15.9	72.9	11.2
		Center 18	4147	29.5	17.7	68.4	13.9
		Center 19	726	20.2	3.1	39.8	57.2
		Center 24	2859	23.7	15.1	63.9	21.0
		Center 25	924	26.1	8.8	79.3	11.9
Oct07-Dec07	Days of life 1-14	All centers	9201	32.1	9.3	76.8	14.0
		Center 3	1307	35.6	8.5	77.5	14.0
		Center 5	1741	32.6	7.7	70.9	21.4
		Center 16	2182	42.1	9.8	84.1	6.0
	Day 15 to 36 wks	All centers	44909	25.6	12.9	65.8	21.3
		Center 3	4597	33.0	14.2	69.4	16.4
		Center 5	8024	23.3	10.4	61.3	28.3
		Center 11	1144	24.5	10.2	54.2	35.6
		Center 12	1573	28.6	7.1	63.9	29.0
		Center 14	1386	20.9	13.3	63.9	22.8
		Center 15	2869	23.6	17.7	64.7	17.5
		Center 16	7243	26.1	14.6	70.7	14.7
		Center 18	1585	26.0	15.7	72.9	11.5
		Center 23	2680	28.8	10.8	61.4	27.8
		Center 25	6171	24.5	9.6	73.3	17.1
Jul07-Sep07	Days of life 1-14	All centers	14848	33.9	7.5	76.0	16.5
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1404	34.6	9.6	74.6	15.8
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9
		Center 16	1171	39.5	7.4	81.3	11.3

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent
		Center 23	2150	32.6	5.5	71.6	23.0
		Center 25	1723	39.7	5.9	83.1	11.0
	Day 15 to 36 wks	All centers	55927	25.4	11.3	65.7	22.9
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5767	21.0	9.5	59.7	30.8
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	14970	34.4	9.1	76.7	14.2
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1062	31.1	11.5	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1439	40.3	8.5	85.7	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	685	16.3	7.9	69.3	22.8
	Day 15 to 36 wks	All centers	56188	28.5	12.2	66.0	21.9
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8
		Center 9 site B	3605	43.6	12.1	77.4	10.5

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >97
		Center 11	4086	23.7	10.1	57.7	32.2
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	4710	29.9	13.1	69.8	17.1
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2857	22.4	9.4	55.4	35.2
Jan07-Mar07	Days of life 1-14	All centers	16812	35.4	8.3	78.1	13.6
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	54926	27.9	12.5	68.9	18.6
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8
		Center 16	3353	30.8	14.5	69.2	16.3

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 22	689	31.4	7.8	68.3	23.9
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	4307	20.2	17.7	64.5	17.8
Mar06-Dec06	Days of life 1-14	All centers	32802	37.2	8.2	79.0	12.9
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2419	33.1	9.1	67.5	23.4
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5667	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	881	30.5	6.0	77.5	16.6
		Center 25	1138	48.0	6.4	83.5	10.1
	Day 15 to 36 wks	All centers	106915	29.2	12.5	68.4	19.1
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3278	29.7	11.8	72.9	15.3
		Center 11	5915	29.9	10.4	61.4	28.2
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14390	29.2	12.5	69.1	18.5
		Center 18	14879	24.1	17.0	66.3	16.8
		Center 19	1695	24.5	7.9	56.8	35.3
		Center 25	6484	39.9	9.3	77.0	13.7

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 08/23/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent
Through Feb06	Days of life 1-14	All centers	27099	38.1	9.3	79.6	11.1
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1448	32.0	10.0	77.5	12.5
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1517	42.1	9.5	85.5	5.0
		Center 22	3586	40.3	8.6	80.1	11.3
	Day 15 to 36 wks	All centers	132749	26.5	12.2	67.6	20.2
		Center 3	13570	17.7	17.4	64.2	18.4
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	4802	17.3	8.5	58.1	33.4
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	8688	28.1	17.8	63.6	18.6
		Center 19	1280	35.4	7.7	77.5	14.9
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	3563	29.6	16.7	68.7	14.6
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

From: Huitema, Carolyn Petrie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Study Adverse Events
Date: Wednesday, September 03, 2008 1:42:20 PM

Thanks, Rose.
Then this is what I am working on!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 03, 2008 1:40 PM
To: Huitema, Carolyn Petrie
Subject: Fw: NICHD NRN Support Study Adverse Events

Here is the AE info - I had asked that a table be generate to look at the cumulative data
---
Sent from my BlackBerry Wireless Handheld

From: Zaterka-Baxter, Kristin
To: Das, Abhik ; Gantz, Marie ; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Cunningham, Meg
Sent: Fri Aug 29 08:19:53 2008
Subject: FW: NICHD NRN Support Study Adverse Events
Please see below.
Thanks,
Kris

From: Gordon Avery [mailto:gavery123@gmail.com]
Sent: Friday, August 29, 2008 7:09 AM
To: Zaterka-Baxter, Kristin
Subject: Re: NICHD NRN Support Study Adverse Events

Single events of pneumothorax are sufficiently common in these tiny babies not to require a specific response. Only if there is a trend when viewed statistically would I involve the Committee. Best. Gordon Averfy

On Thu, Aug 28, 2008 at 4:04 PM, Zaterka-Baxter, Kristin <kzaterka@rti.org> wrote:

Hi Dr. Avery,

Dr. Higgins asked that I send you these two recent Support Study adverse events (1. pneumothorax; 2. pneumothorax and eventual death) that were felt to be possibly related to study by the site PI. The reports are attached. In addition:

1. The pneumothorax event that occurred at Center 12 (Indiana) did not require IRB notification as it is not unexpected and did not meet their criteria for reporting (serious, related and *unexpected*) events.

2. The pneumothorax event that occurred at Center 9 (Emory) was reported to their IRB per institutional policy; we were notified today that this infant died (b) (6) and an updated report was sent detailing the events leading to death (autopsy pending).

Thanks and please let me know if you have any question or require further information

Kris Zaterka-Baxter

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Kris Zaterka-Baxter

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3040 Cornwallis Road

RTP, NC 27709 USA

From: Huitema, Carolyn Petrie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Emory AE
Date: Wednesday, September 03, 2008 1:34:48 PM

Ok. I am helping Kris while she is away and did not want anything to fall through the cracks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 03, 2008 1:32 PM
To: Huitema, Carolyn Petrie
Subject: Re: Emory AE

Yes, Kris sent this to Dr. Avery last week
He said it is related to prematurity.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Huitema, Carolyn Petrie
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Sep 03 13:29:36 2008
Subject: Emory AE
Just tried calling.

I have an AE from Emory that may attribute death to SUPPORT study, autopsy pending. Do you have this report?

Network ID (b) (6) faxed (b) (6) .

Carolyn Huitema

Research Analyst
RTI International
(301) 270-6664
petrie@rti.org

From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee for October
Date: Thursday, August 28, 2008 4:38:24 PM

There's a SUPPORT called scheduled Fri 9/12 from 1-2pm ET.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 28, 2008 2:52 PM
To: Webb, Robin E.
Subject: RE: SUPPORT Subcommittee for October

WE need to try another time – do you have a SUPPORT Subcommittee call in advance of the SC meeting? I think if this is already scheduled, we can do it then

Rose

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Thursday, August 28, 2008 2:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee for October

I've heard from everyone but Wade Rich.

Newman, Walsh, and Yoder are not available on 10/8

Archer, Das, Faix, Finer, Gantz and Schibler can do 11-12pm ET. We'll lose Laptook since he'll only be in until 10:30. Carlo is in Dubai but said he could call in, although I'm not sure what the difference and if 11am ET will work for him.

Do you want to schedule the call for this time? Or try something else?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 28, 2008 10:14 AM
To: Webb, Robin E.
Subject: RE: SUPPORT Subcommittee for October

All day (As early as 8-8:30 am)

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Thursday, August 28, 2008 10:13 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee for October

Rose,

What time are you available on 10/8?

Thanks,
Robin

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

Sent: Monday, August 25, 2008 8:31 PM
To: Webb, Robin E.
Subject: Fw: SUPPORT Subcommittee for October

Sent from my BlackBerry Wireless Handheld

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Aug 25 19:44:38 2008
Subject: RE: SUPPORT Subcommittee for October
Rose
Oct 7 3-5 if fine (b) (6) and I will only be in for a few hours in the morning (need to leave by 10:30am). AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 2:18 PM
To: Webb, Robin E.; Abbot Laptook; Bradley Yoder; adas@rti.org; mgantz@rti.org; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee for October

The dates are wrong – PLEASE SEND ROBIN Availability for 10/8 (Not 9/8)

Sorry for the confusion

Rose

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Monday, August 25, 2008 2:03 PM
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: Webb, Robin E.; sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; msumner@peds.uab.edu; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT Subcommittee for October

We'd like to schedule a SUPPORT Subcommittee call prior to the SC meeting. Please let me know your availability for the days below, indicating time zone if other than ET.

Thanks,
Robin

Tues 9/7 3-5 PM
Wed 9/8

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: question regarding data on GDB and SUPPORT
Date: Wednesday, August 27, 2008 4:29:28 PM

Good point – technically no: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c1

I'll ask Missy to ask this of her IRB; I'm not sure where the 12 hours came from in the first place but it sounds like it was their IRB that put this stipulation in.

Thanks !
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 27, 2008 4:17 PM
To: Zaterka-Baxter, Kristin
Subject: RE: FW: question regarding data on GDB and SUPPORT

If the infant dies, then it is no longer considered human subjects research, correct?

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, August 27, 2008 4:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: question regarding data on GDB and SUPPORT

I didn't see anything in the protocol or MOP that actually defines it so I suggested she follow what her IRB calls neonatal death and it sounds like that is <12 hours, which would mean she would need to approach the mom for verbal consent and I'm not sure she wants to do that because of the sensitive nature of things so we might not get GDB data on baby B. I think she was hoping for an NICHD ruling that would override the sites calling...

Thanks,

Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 27, 2008 4:12 PM
To: Zaterka-Baxter, Kristin
Subject: RE: FW: question regarding data on GDB and SUPPORT

It is still a neonatal death, isn't it?

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, August 27, 2008 4:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: question regarding data on GDB and SUPPORT

I think missy is having a consent dilemma; if she calls baby B (with death at ~36 hrs) a 'neonatal death' then her IRB does not require her to get verbal consent for GDB (as she does ***not*** have to for baby A); if baby B is not considered to be a 'neonatal death' then she will need to ask the parents for verbal consent to collect GDB data.

Thanks,

Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 27, 2008 3:56 PM
To: Zaterka-Baxter, Kristin; Melissa Leps
Cc: [SCRN] Stoll, Barbara; Ellen Hale
Subject: RE: FW: question regarding data on GDB and SUPPORT

Baby A – death within 12 hours,

Baby B – death after 12 hours, so fill out appropriate forms

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, August 27, 2008 3:34 PM
To: Melissa Leps
Cc: Higgins, Rosemary (NIH/NICHD) [E]; [SCRN] Stoll, Barbara; Ellen Hale
Subject: RE: FW: question regarding data on GDB and SUPPORT

Hi Missy,

I would go by what your institution classifies as a 'neonatal death'; the GDB does not define neonatal death in the MOP or protocol. I've copied Rose, Barbara and Ellen in case I've missed something or there are other opinions.

Thanks,

Kris

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Wednesday, August 27, 2008 11:29 AM
To: Zaterka-Baxter, Kristin
Subject: Re: FW: question regarding data on GDB and SUPPORT

Kris,
I've read everyone's responses and thank you for your help; however, I have another question :)
Do I count both of the infants as Neonatal Deaths? Technically, this is for infant's that die within the first 12 hours. One of the infants did not die in that time frame. The situation is very delicate and I am would have to get verbal consent from the mom to gather the info on the infant that lived longer than 12 hours, per our IRB unless I count (b) (6) as a Neonatal Death, and in that case, the info can be gathered without any consent.

This infant lived ~36 hours, but no care was provided. The infant was actually in the room with mom, per family request and not in the unit.

Thanks

Missy Leps, RN
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206(b) (6)
fax: 214.648.2481

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 8/26/2008 1:11 PM >>>

Does this answer your questions – I needed to consult the higher power – couldn't answer alone.

Thanks,

Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 26, 2008 2:03 PM
To: Zaterka-Baxter, Kristin; Melissa Leps
Cc: Ellen Hale; Barbara Stoll
Subject: RE: question regarding data on GDB and SUPPORT

Both qualify for GDB

ROse

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, August 26, 2008 1:47 PM
To: Melissa Leps
Cc: Ellen Hale; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: question regarding data on GDB and SUPPORT

Hi,

Please see Missy's case below re. twins and GDB data collection. Based on the GBD criteria (below) I think both infants are eligible for GDB data collection and as far as consent, she should follow her IRB guidelines thought it sounds like these are both considered neonatal deaths so verbal consent may not be required; please let me know how you think Missy should proceed with these cases:

3.1.1 Eligibility

All infants who are 1) inborn and between 401 grams and 1000 grams inclusive birth weight and/or 2) inborn and between 22 0/7 to 28 6/7 weeks (<29 weeks) inclusive gestational age are eligible for the study. Infants enrolled in a Network RCT or prospective observational study (inborn and transferred infants) may be included in the GDB dataset if requested by the study subcommittee and approved by the NRN Steering Committee. These may be otherwise premature and/or low birth weight infants outside the GDB gestational and birth weight criteria. In addition, all inborn, liveborn infants who meet the above criteria and die prior to admission to the NICU are enrolled posthumously.

Thanks,

Kris

From: Melissa Leps [mailto:Melissa.Leps@UTSouthwestern.edu]
Sent: Tuesday, August 26, 2008 12:05 PM
To: Zaterka-Baxter, Kristin
Subject: question regarding data on GDB and SUPPORT

Kris,
I have a question and was not sure who to ask. Nancy is on vacation for quite a while, so I thought I'd see what you thought I should do.
(b) (6) Dates for mom were very inconsistent. She had 1st prenatal care late--19-20 weeks. Her dates by LMP were 21-22 weeks. By sono, 23-24 weeks. We consented her for SUPPORT when she was 23.6 or (b) (6)
Her OB gave her steroids, which here (b) (6) NEVER give steroids unless it's a private pay patient or the mom is 25+ weeks.

So on Friday, they did another sono and redated her making her 24.0 weeks on (b) (6)
She delivered that night. They did randomize the infants to the same arm of SUPPORT, baby "A" delivered, they gave some O2 because there was no respiratory effort. The fellow did the Ballard and the infant's exam showed 22 weeks. Decision was made to provide comfort care only. Twin B delivered after this decision was made, so no resuscitation efforts were made for this infant at all. Comfort care was provided to both infants.

So, a big question I have has to do with the GDB data. Twin B's time of death was within 6 hours of birth. Twin A's time of death was after 12 hours of birth. So on this infant do I complete the regular GDB paperwork? not the NG03?
FYI-for GDB data collection here we are required to get a verbal consent. On neonatal deaths, we are not required to get a verbal consent; however, this infant lived for >24 hours. How should I handle this?

Thanks,

Missy Leps, RN
Department of Pediatrics
Division of Neonatal/Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., E3.404-B
Dallas, Texas 75390-9063
melissa.leps@utsouthwestern.edu
office: 214.648.3780
pager: 972.206.(b) (6)
fax: 214.648.2481

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Shirley Cosby; Monica Collins; Myriam Peralta, M.D.
Cc: adas@rti.org; Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, August 26, 2008 5:51:06 PM

(b) (6) did not have any follow up eye exam after d/c. Lost to fu at 55 wks completed.
(b) (6) requesting results from retinal specialist
(b) (6) 18 month follow up visit completed last week. It should be in this week's transmission.
(b) (6) entered missed form NF09a in computer today
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 11:14 AM
To: Wally Carlo, M.D.; Shirley Cosby; Monica Collins; Myriam Peralta, M.D.; Vivien Phillips
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT Outcomes. Let us know how you are doing.
This is truly amazing given the high level of recruitment at UAB!!!
Thanks for all the hard work!!!!

Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
16	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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National Institutesof Health
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bridge, Renee
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: wrich@ucd.edu
Subject: support forms ucsd
Date: Tuesday, August 26, 2008 1:53:07 PM

Hi, I just finally completed patient number (b) (6) and I finally found where patient (b) (6) was followed for ROP, should have that info soon. Sorry, I am so slow. Thanks. Renee

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Angelita Hensman; Zaterka-Baxter, Kristin
Cc: alaptook@WIHRI.org
Subject: RE: Surrogate mom
Date: Tuesday, August 26, 2008 12:08:03 PM

I agree with Rose. If the surrogate has legal authority to consent for the infants before birth then she can be consented. I would also want the legal parents to agree and consent, preferably before birth.
In our hospital we would only enroll if both surrogate and legal parents consented.
If there is uncertainty, we would not approach.
Hope this helps
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 26, 2008 6:06 AM
To: Angelita Hensman; Zaterka-Baxter, Kristin; Finer, Neil
Cc: alaptook@WIHRI.org
Subject: RE: Surrogate mom

This involves the person who can "legally consent" in this situation. We also need ongoing data collection and follow up. If the IRB is ok with it and the "legal guardian" of the babies is ok, you can enroll them. If you have concerns, then don't enroll them. "parent not available" is acceptable is you do not enroll them.

Rose

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Tuesday, August 26, 2008 9:02 AM
To: Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Surrogate mom

Should we try to enroll a (b) (6) into the SUPPORT study?

Still waiting for the IRB to give us some consent guidelines as well.

Thanks
Angelita

401-274-1122 x 1730

From: Zaterka-Baxter, Kristin
To: keszlerm@gunet.georgetown.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: NICHD NRN Support Trial DSMC review October 7, 2008
Date: Tuesday, August 26, 2008 9:34:19 AM

Dr. Keszler,

Please accept my apology for not sending you this email initially. We are requesting a time block from 10:00 am to 12:00 pm on Oct 7, 2008 for the NICHD NRN Support study DSMC review (please see below). Please let me know if you are available to meet during this time.

Thanks much,
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, August 25, 2008 4:02 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Hi all,

We would like to solidify the timeframe for the next Support Study DSMC meeting to be held in Rockville MD on October 7, 2008. We anticipate needing 2 to 3 hours for this meeting; there was only one preference for time that day and it was for morning hours. We would like to propose 10:00 am to 12:00 pm EST with lunch served afterwards (*1:00 – 3:00 pm PCT* and *3:00 – 5:00 pm UK* time for folks calling in).

Please let me know if there are any objections and please note the meeting agenda and interim report will be sent out later next week.

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Wednesday, June 18, 2008 5:22 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Hi everyone,

The next meeting for review of the Support trial interim analysis at 75% status will be held on **Tuesday October 7, 2008 at the RTI office in Rockville, MD** (Time TBD so please send preferences). The study report will be sent one month before the meeting for your review. If you can not attend the meeting, we would very much appreciate your comments/suggestions on the materials send before the meeting so that we can distribute those to the group. We will have an international, operator assisted teleconferencing system to contact folks who will join the meeting by phone. Details and the meeting

agenda will be sent out with the study report.

Thanks all for your patience while were trying to find an available time to meet. Please let me know if you have any questions.
Kris

Kris Zaterka-Baxter
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(tel) 919-485-7750
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kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: FW: NICHD NRN Support Trial DSMC review October 7, 2008
Date: Tuesday, August 26, 2008 8:41:14 AM

Rose:

We queried these guys repeatedly before setting up this meeting. In fact, I dont think I have ever seen (b) (6) attend an NRN DSMC meeting in the last few years (other than once by phone, and that too not for the whole time). I think you may want to look for another OB representative on our DSMC who would have a greater commitment to the NRN.

Thanks

Abhik

From: Mike Ross [mailto:mikeross@ucla.edu]
Sent: Monday, August 25, 2008 7:26 PM
To: Zaterka-Baxter, Kristin; gavery123@gmail.com; RJB6J@hscmail.mcc.virginia.edu; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; tclemons@emmes.com; kant@unc.edu; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; blaisdellcj@nhlbi.nih.gov
Cc: meganhb@u.washington.edu; Price, Bonnie; Das, Abhik; Gantz, Marie; higginsr@mail.nih.gov; nfiner@ucsd.edu; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

I will be out of the country.

Michael Ross

Michael G. Ross, M.D., M.P.H.
Professor and Chair
Dept of Obstetrics and Gynecology
Harbor-UCLA Medical Center
Geffen School of Medicine at UCLA
tel 310 222 3544

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, August 25, 2008 1:02 PM
To: gavery123@gmail.com; RJB6J@hscmail.mcc.virginia.edu; Christine A. Gleason; Willinger, Marian (NIH/NICHD) [E]; tclemons@emmes.com; mikeross@ucla.edu; kant@unc.edu; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; blaisdellcj@nhlbi.nih.gov
Cc: meganhb@u.washington.edu; bprice@obgyn.humc.edu; Das, Abhik; Gantz, Marie; higginsr@mail.nih.gov; nfiner@ucsd.edu; Monica Bocaner; Cunningham, Meg; Rich, Wade
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Hi all,

We would like to solidify the timeframe for the next Support Study DSMC meeting to be held in Rockville MD on October 7, 2008. We anticipate needing 2 to 3 hours for this meeting; there was only one

preference for time that day and it was for morning hours. We would like to propose 10:00 am to 12:00 pm EST with lunch served afterwards (*1:00 – 3:00 pm PCT* and *3:00 – 5:00 pm UK* time for folks calling in).

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Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Wednesday, June 18, 2008 5:22 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'; Das, Abhik; Gantz, Marie; 'higginsr@mail.nih.gov'; 'nfiner@ucsd.edu'; 'Monica Bocaner'; Cunningham, Meg; 'Rich, Wade'
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

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Thanks all for your patience while were trying to find an available time to meet. Please let me know if you have any questions.
Kris

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RTP, NC 27709 USA

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; "Walsh, Michele"
Subject: RE: SUPPORT OUTCOMES
Date: Monday, August 25, 2008 2:38:32 PM

Both are done, but our network computer is with James at RTI on death watch.

Bonnie

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, August 25, 2008 1:17 PM
To: bss5@case.edu
Subject: FW: SUPPORT OUTCOMES

Michele Walsh
beeper(b) (6)
Ph 216 844 5109

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 12:03 PM
To: Michelle Walsh; nancy newman
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT Outcomes. Let us know how you are doing.
This is amazing given your high level of recruitment!!!
Thanks for all the hard work!!!!

Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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National Institutesof Health
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Ellen.Hale@oz.ped.emory.edu
Subject: RE: SUPPORT
Date: Monday, August 25, 2008 1:08:25 PM

Sorry, Ellen, what I said below is true, but it does not answer your question which was about reminders for FU forms, not for ROP status. The reason you received that message was that the NF10 said FU had been completed but we did not have the NF05 and NF09a entered yet. The message was just because of that inconsistency. Obviously the forms are not late yet! Let me know if you have any other questions.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

919-554-8355

From: Gantz, Marie
Sent: Monday, August 25, 2008 1:04 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Ellen.Hale@oz.ped.emory.edu'
Subject: RE: SUPPORT

Hi Ellen,

To answer your question about why you are receiving messages about kids whose FU window are still open – we received a request to remind centers in advance when the ROP outcome needs to be obtained at the FU visit. So, the reminders will start a month before the window opens. Let me know if you have any other questions.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

919-554-8355

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 12:51 PM
To: Gantz, Marie
Subject: FW: SUPPORT

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Monday, August 25, 2008 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

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

Hi,

We are missing a few SUPPORT Outcomes. Let us know how you are doing.

Thanks for all the hard work!!!

Rose

CENTER	NETWORK	ROP_message
9	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Mother has not returned our calls.

CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed Cannot locate. Will code as lost to follow up

9 (b) (6)

FU window has closed but NF05 and NF09a have not been completed

Family lives in Savannah. They have been unable to keep appointments. We are planning a home visit.

9 (b) (6)

FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed

Child was seen last week. We will enter rest of forms prior to end of month. (Why are we receiving emails about children who still have their windows open?)

9

FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed
Child was seen this month. We will enter rest of forms prior to end of month.

Rosemary D. Higgins, MD

Chair, Publications Committee, Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

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Bethesda, MD 20892

For overnight delivery Use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Betty Vohr
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, August 25, 2008 12:43:56 PM

Rose,
I may be late for the conference call since I have to go out of the hospital for an important meeting about my funding from CVS charitable trust. We have had difficulty setting up a meeting that is convenient for the funders. Joyce is typing a brief summary of my comments and I will forward to you.
Betty

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 25, 2008 12:12 PM
To: Abbot Laptook; Angelita Hensman; Betty Vohr
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few SUPPORT Outcomes. Let us know how you are doing.
This is amazing given your recruitment!!
Thanks for all the hard work!!!!

Rose

CENTER	NETWORK	BPD_message
14	(b) (6)	PHY01 is expected based on NG07 but has not been entered
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
14	[redacted]	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes report
Date: Thursday, August 21, 2008 3:00:30 PM
Attachments: Infants with missing outcomes 08-21-08.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
9		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
16		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
16		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient's follow-up window has closed and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient is within their Fol-up window and final ROP status has not been reported.
18		The patient's follow-up window will open within the next month and final ROP status has not been reported. Please obtain final ROP status at the Follow-up visit.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		The patient's follow-up window has closed and final ROP status has not been reported.
19		The patient's follow-up window will open within the next month and final ROP status has not been reported. Please obtain final ROP status at the Follow-up visit.
19		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
19		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: FW: ancillary to SUPPORT trial
Date: Thursday, August 14, 2008 4:33:47 PM
Attachments: hgt2.vcf

Our vote is to go ahead with the Object permanence secondary-
As it is low cost and may be informative. See comments below.

Michele Walsh
beeper(b) (6)
Ph 216 844 5109

From: Hudson Taylor [mailto:hudson.taylor@case.edu]
Sent: Thursday, August 14, 2008 2:36 PM
To: Walsh, Michele
Cc: Hack, Maureen ; H. Gerry Taylor; hgf@case.edu
Subject: Re: FW: ancillary to SUPPORT trial

Michele:

I think the idea of relating attainment of object permanence at a certain age to brain status and later scores on the Bayley and on test of executive function is a reasonable, as object permanence is a major early cognitive milestone. I also think that there are sufficient numbers of cases not to have to worry about statistical power. The amount of extra effort involved is that for coding and entering scores for 3 or so items from the Bayley. So there's some cost but it's not excessive. This is assuming that the MRIs and tests of executvie function are given as part of the overall project and are not being proposed specifically for the proposed study.

My questions about the proposed study are as follows:

1. How strong is the evidence relating attainment of object permanence at an earlier vs later age to cognitive and brain development? My guess is that there may be some evidence, but that it may not be unequivocal.

2. What are the chances that measuring attainment of object permanence at the age at which the Bayley was given as part of the Neonatal Follow-up Network project (I assume the applicants are proposing to use the 20 month Bayleys) is going to be useful. I would think that there would be a certain optimal age for measuring this and that this age might be one at which about half of the population attained object permanence and half did not--or something close to this. However, I'm not sure what case the applicants have made for 20 months being close to this optimal age. If most children either do or don't attain object permanence by 20 months, then the study will not tell us anything.

3. To what extent do the 3 items taken from the Bayley provide a valid assessment of object permanence?

4. Is there any preliminary data, if only from the applicant's own site, to suggest measurement of object permanence as proposed can be reliably assessed and/or may in fact predict later developmental outcomes.

So my bottom line is that this proposal makes sense but that there's some unanswered questions as to whether or not it will tell us anything. Of course, if it does turn out that an early measure of cognitive development has validity in predicting later development or is related to brain status, that would be important. I guess I'm a little skeptical (at least without some preliminary support) that assessing 3 items from the Bayley would be that powerful.

Hope this helps,

Gerry

----- Original Message -----
From: "Walsh, Michele" <Michele.Walsh@UHhospitals.org>
Date: Wednesday, August 13, 2008 10:04 am
Subject: FW: ancillary to SUPPORT trial
To: "Hack, Maureen " <Maureen.Hack@UHhospitals.org>, "H. Gerry Taylor" <hgt2@case.edu>, hgf@case.edu

> Could you please look at the attached protocol and
> give me your opinion on its worth. The background
> on this is that the Network Follow Up Investigators
> have been asked to generate hypothesis testing protocols,
> rather than continue to do generic neurocognitive evaluations.
> They are just beginning their efforts. I want to be supportive,
> but only for projects that will answer good questions, not silly ones!
> I am unsure of which group this proposal falls into.
> Thanks
>
> Michele Walsh
>
> beeper(b) (6)
>
> Ph 216 844 5109
>
>
>
> _____
>
> From: Higgins, Rosemary (NIH/NICHD) [E]
> [mailto:higginsr@mail.nih.gov]
> Sent: Wednesday, August 06, 2008 5:08 PM
> To: Neil_Finer" <; Rich, Wade; Michelle Walsh; wacarlo@uab.edu;
> Bradley.yoder@hsc.utah.edu; Roger Faix; Abbot Laptook;
> kurt.schibler@cchmc.org; Das, Abhik; Gantz, Marie; nancy newman
> Cc: Susan Hintz; Webb, Robin E.; Zaterka-Baxter, Kristin; Cunningham,
> Meg; Huitema, Carolyn Petrie; Newman, Jamie
> Subject: FW: ancillary to SUPPORT trial
>
>
>
> Attached is a SUPPORT secondary study for consideration. We will

> haveRobin set up a call.
>
>
>
> Thanks
> Rose
>
>
>
> _____
>
> From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
> Sent: Tuesday, August 05, 2008 1:31 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Janell Fuller; Jean Lowe; Susan Hintz
> Subject: ancillary to SUPPORT trial
>
>
>
> Hi, Rose. I am attaching a revised proposal for our ancillary
> study to
> SUPPORT, "Evaluation of early working memory in extremely preterm
> infants", and our responses to the reviewers of the first version.
> (I'malso happy to report that our manuscript on early working
> memory as
> assessed by object permanence has been accepted by the Journal of
> ChildNeurology).
>
>
>
> You will notice that Susan Hintz has been added to the protocol
> development group. She has reviewed our revisions, made several great
> suggestions, and is enthusiastic about the protocol. We would of
> coursewelcome others, if this is approved and goes forward.
>
>
>
> Let me know if you need anything else, or have suggestions for us
> beforesending on to the SUPPORT subcommittee.
>
>
>
> Thanks, Kristi
>
>
>
> Visit us at www.UHhospitals.org.
>
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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008
Date: Wednesday, August 13, 2008 12:01:40 PM

Thanks Rose.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 13, 2008 9:00 AM
To: Rich, Wade
Cc: Finer, Neil; Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Here is the phototherapy PAS abstract submission for the late breakers for 2007

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Wednesday, August 13, 2008 11:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

do u have the abstract?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 13, 2008 8:54 AM
To: Rich, Wade; Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

The second revision was re-sent to NEJM almost 3 weeks ago – we are anxiously waiting and I will let folks know once we hear something.

Rose

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Wednesday, August 13, 2008 11:52 AM
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Trial DSMC review October 7, 2008

Kris,
Neil asked me current status of Phototherapy Abstract/publication. Do you know?
wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, June 18, 2008 2:22 PM
To: gavery123@gmail.com; RJB6J@hscmail.mcc.virginia.edu; Christine A. Gleason; Willinger, Marian (NIH/NICHD) [E]; tclemons@emmes.com; mikeross@ucla.edu; kant@unc.edu; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; blaisdellcj@nhlbi.nih.gov
Cc: meganhb@u.washington.edu; bprice@obgyn.humc.edu; Das, Abhik; Gantz, Marie; higginsr@mail.nih.gov; Finer, Neil; Monica Bocaner; Cunningham, Meg; Rich, Wade
Subject: NICHD NRN Support Trial DSMC review October 7, 2008

Hi everyone,

The next meeting for review of the Support trial interim analysis at 75% status will be held on **Tuesday October 7, 2008 at the RTI office in Rockville, MD** (Time TBD so please send preferences). The study report will be sent one month before the meeting for your review. If you can not attend the meeting, we would very much appreciate your comments/suggestions on the materials send before the meeting so that we can distribute those to the group. We will have an international, operator assisted teleconferencing system to contact folks who will join the meeting by phone. Details and the meeting agenda will be sent out with the study report.

Thanks all for your patience while were trying to find an available time to meet. Please let me know if you have any questions.
Kris

Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
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Federal Express/UPS/DHL Shipping Address:
Kris Zaterka-Baxter
RTI International
3040 Cornwallis Road
RTP, NC 27709 USA

From: Katherine A Foy
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Michael Cotten; Ronald N Goldberg; Ricki F Goldstein; lohme001@mc.duke.edu; Gantz, Marie
Subject: Re: SUPPORT
Date: Tuesday, August 05, 2008 3:37:06 PM

I am still working on these. I am trying to find out where they had follow-up appointments. Once I get the information, I will put it into the system.
Thank you,

Kathy Foy, RN
Clinical Research Coordinator
Duke University Health Systems
Neonatology
681-5859 office
970-1421 pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 07/29/2008 11:42 AM

To: "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Katherine A Foy" <foy00004@mc.duke.edu>, <lohme001@mc.duke.edu>

cc: "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>

Subject: SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER NETWORK ROP_message

19 (b) (6) The patient's follow-up window has closed and final ROP status has not been reported.

19 (b) (6) No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

19 (b) (6) SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.

19 (b) (6) 55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.

CENTER NETWORK BPD_message

19 (b) (6) Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

19 (b) (6) Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

CENTER NETWORK FU_message

19 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed

19 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed

19 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Gantz, Marie
To: Phelps, Dale
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: question
Date: Monday, August 04, 2008 2:56:11 PM

I agree.

Marie

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

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, August 04, 2008 2:55 PM
To: Gantz, Marie
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: question

Thanks Marie,
This long time (17 months) is not because of the disease (I'm pretty sure) but because of the re-examination schedules, and missed exams that occurs as an outpatient.

Dale

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, August 04, 2008 2:34 PM
To: Phelps, Dale
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: question

Hi Dale,

Abhik forwarded me your message so I could respond. Your additions in brackets are correct. I would only add that after looking at the data we had as of last month it has taken us up to 17.5 months to obtain ROP status on infants with favorable status (I had found 15-16 months previously). We still have 95% of those with favorable status by around 8 months.

Marie

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

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, August 04, 2008 12:06 PM
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: question

Thank you... Please tell me if I have it right now. [my additions in brackets]. I added the things I had to figure out so I won't have to go back and figure them out again later.
Dale ☺

From: Gantz, Marie
Sent: Wednesday, May 14, 2008 5:14 PM
To: Das, Abhik
Subject: RE: question

According to numbers I have from a while back, the median time to get ROP status is about 13 weeks [after birth, or close to term due date] (11 if the infant has ROP, 14 if not). For infants with ROP, we [finally] have ROP status for everyone [all enrolled who survived] by [3 months later,] around 6-7 months after birth, but for infants without ROP it has taken up to 15-16 months [after birth], although we get 95% by around 8 months.

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, August 04, 2008 11:51 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: FW: question

Dale:
Marie tells me that the weeks and months described below are both post-birth.

Thanks

Abhik

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, August 01, 2008 9:05 AM
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: question

Hi Abhik, I'm looking at these data and am now somewhat uncertain:

In this very interesting statement, you use the words weeks and months, but I'm not sure which they are.

Weeks: are these weeks after birth? Or are they weeks post-menstrual age ? (PMA = gestational age plus chronologic age)

I'm pretty sure you mean weeks chronologic age.

That would be consistent with what I expect, that these infants born around 26 weeks would be 26+13 = 39 weeks when reaching an ROP outcome if it were to be an unfavorable one. (good outcomes take much longer).

Months: are these months after birth? Or are they corrected age months (months after due date)?

Or ... the 6-8 months (if corrected age), does not match with 12-14 weeks of

chronologic age. (which would be about 0-1 months corrected)

The 6-8 months, if chronologic age, does not match with 12-14 weeks of chronologic age (which would be 3 months corrected).

I would expect final unfavorable status to actually occur by 36 -52 weeks PMA (52 weeks PMA is about 3 months corrected)

I would expect final favorable status to actually occur by 38-52 weeks PMA, or maybe longer.

Of course, when it happens physiologically, and when an examination happens to document it often occur at different times. That may be the explanation.

Dale

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, May 15, 2008 8:58 AM
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: question

FYI

From: Gantz, Marie
Sent: Wednesday, May 14, 2008 5:14 PM
To: Das, Abhik
Subject: RE: question

According to numbers I have from a while back, the median time to get ROP status is about 13 weeks (11 if the infant has ROP, 14 if not). For infants with ROP, we have ROP status for everyone by around 6-7 months, but for infants without ROP it has taken up to 15-16 months, although we get 95% by around 8 months.

From: Das, Abhik
Sent: Wednesday, May 14, 2008 4:39 PM
To: Gantz, Marie
Subject: question

What is the approx. median time it is taking us to determine ROP in Support?

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

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Monday, August 04, 2008 9:49:32 AM

Final ROP status does show up for the two infants listed below. The data were transmitted to RTI the week after the missing data reports were run.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
[illegible]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 11:53 AM
To: Gantz, Marie
Cc: Das, Abhik
Subject: FW: SUPPORT

Can you look to see if the ones that were entered show up?

From: Bonnie Siner [mailto:bss5@case.edu]
Sent: Tuesday, July 29, 2008 11:31 AM
To: 'Walsh, Michele'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose,
Please direct these inquiries to me.
Thanks, Bonnie Siner

(b) (6) still tracking
already entered
already entered

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, July 29, 2008 10:54 AM
To: bss5@case.edu
Subject: FW: SUPPORT

Bonnie: pls update and copy me on the results.

Michele Walsh
beeper(b) (6)
Ph 216 844 3109

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 10:47 AM
To: Michelle Walsh; nancy newman
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!! Given your outstanding recruitment, this is incredible and deserves a huge pat on the back!!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

Visit us at www.UHhospitals.org.

From: Mcdavid, Georgia E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, August 01, 2008 12:25:45 AM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 7/29/2008 10:40 AM
To: Kennedy, Kathleen A; Tyson, Jon E; Mcdavid, Georgia E
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,

We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!! Also, Brenda Morris was listed as the site PI for SUPPORT - can you tell me which investigator is taking the lead for SUPPORT at UT Houston?
Rose

CENTER

NETWORK

ROP_message

18

(b) (6)

The patient's follow-up window has closed and final ROP status has not been reported.

18

(b) (6)

The patient's follow-up window has closed and final ROP status has not been reported.

18

(b) (6)

The patient's follow-up window has closed and final ROP status has not been reported.

18

(b) (6)

The patient's follow-up window has closed and final ROP status has not been reported.

18

(b) (6)

The patient is within their Fol-up window and final ROP status has not been reported.

18

(b) (6)

The patient is within their Fol-up window and final ROP status has not been reported.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

18

(b) (6)

Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

CENTER

NETWORK

FU_message

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Das, Abhik; Gantz, Marie; Hamer, Faithe Angeline
Subject: RE: SUPPORT
Date: Wednesday, July 30, 2008 2:45:14 PM

Hi. We are aware that this is not completed and are working with outpt ophthalmology to retrieve the records. We will forward them as soon as possible. Thank you-

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.1121 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 11:33 AM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
12		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.

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

From: Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: vanmeurs@leland.stanford.edu; adas@rti.org; mgantz@rti.org
Subject: Re: SUPPORT
Date: Tuesday, July 29, 2008 7:48:41 PM

These data have been keyed and will be transmitted this month.
MBB

Hi,

We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER

NETWORK

ROP_message

15

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

15

(b) (6)

Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

--

Bethany Ball
Division of Neonatal and Developmental Medicine
650.725.8342

From: Bridge, Renee
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT
Date: Tuesday, July 29, 2008 5:52:24 PM

I got your email wrong the first time, sorry. Renee

-----Original Message-----
From: Bridge, Renee
Sent: Tue 7/29/2008 10:26 AM
To: Rich, Wade; higginssr@mail.nih.gov
Subject: RE: SUPPORT

I just recieved the discharge summary from the transfer hospital. To my disappointment no information about ROP status. So, I will seek further. Renee

-----Original Message-----
From: Rich, Wade
Sent: Tue 7/29/2008 9:07 AM
To: Bridge, Renee
Subject: FW: SUPPORT

fyi

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 8:43 AM
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,

We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER

NETWORK

ROP_message

22

(b) (6)

55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD

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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Mackinnon, Brenda
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, July 29, 2008 12:39:27 PM

Hi,
This should be entered before the next report as the baby has been discharged. We enter the last bunch of GDB data at discharge to home.

Thanks,
Brenda

We've performed a little surgery on our name.
Tufts-New England Medical Center is now Tufts Medical Center.
Please update your files with my new contact information. Thank you!

Brenda MacKinnon, RNC, NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box 44
Boston, MA 02111

Beeper #(b) (6)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 11:55 AM
To: Frantz, Ivan; Mackinnon, Brenda; Frantz, Ivan
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!! This is excellent given your recruitment!
Rose

CENTER	NETWORK	BPD_message
23	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

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

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins; Shirley Cosby
Subject: RE: UAB-SUPPORT
Date: Tuesday, July 29, 2008 12:34:05 PM

Way to go!!!

THANKS, Rose.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 10:38 AM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby
Cc: Das, Abhik; Gantz, Marie
Subject: UAB-SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!! Given your outstanding recruitment, this is incredible and deserves a huge pat on the back!!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
16	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, July 29, 2008 11:57:55 AM

Rose:

Marie is (b) (6) this week, so you may not hear from her right away.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 11:53 AM
To: Gantz, Marie
Cc: Das, Abhik
Subject: FW: SUPPORT

Can you look to see if the ones that were entered show up?

From: Bonnie Siner [mailto:bss5@case.edu]
Sent: Tuesday, July 29, 2008 11:31 AM
To: 'Walsh, Michele'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose,
Please direct these inquiries to me.
Thanks, Bonnie Siner

(b) (6) still tracking
(b) (6) -already entered
(b) (6) -already entered

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, July 29, 2008 10:54 AM
To: bss5@case.edu
Subject: FW: SUPPORT

Bonnie: pls update and copy me on the results.

Michele Walsh
beeper (b) (6)
Ph 216 844 5109

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 10:47 AM
To: Michelle Walsh; nancy newman
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!! Given your outstanding recruitment, this is incredible and deserves a huge pat on the back!!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3	[redacted]	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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

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From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, July 29, 2008 11:12:38 AM

Rose,
See our comments below.
Ellen

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Hi

We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!
Rose

CENTER	NETWORK	FU message
	(b) (6)	
9	Bayley will be done 8/1/08	FU marked as complete (per NF10/SF10) but NF09a has not been completed
	(b) (6)	
9	Bayley will be done 8/1/08	FU marked as complete (per NF10/SF10) but NF09a has not been completed
	(b) (6)	
9	Currently lost but still trying to locate.	FU window has closed but NF05 and NF09a have not been completed
	(b) (6)	
	This child lives in (b) (6) and had to reschedule	

and now rescheduled for mom to (b) (6)

g [redacted] EU window has closed but NF05 and NF09a have not been completed

(b) (6)

Seen 7/18 and

g paperwork pending. EU marked as complete (per NF10/SF10) but NF05 and NF09a have not been [illegible]

[redacted]

[redacted]

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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higginsr@mail.nih.gov

[redacted]

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Tuesday, July 29, 2008 11:06:44 AM

I guess Marie can just make a note of this and remove them from her report.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 29, 2008 11:05 AM
To: Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT

What do they need to do to stop the edit?

From: Janet Morgan [mailto:Janet.Morgan@UTSouthwestern.edu]
Sent: Tuesday, July 29, 2008 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

These babies are the twins that we messed up on some time ago and did Bayley II instead of III, we have tried and are unable to get them back as they now lost. We did notify everyone regarding this when it happened, not sure what else to do at this point.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 07/29/08 9:48 AM >>>
Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER	NETWORK	FU_message
4	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed
4	[redacted]	FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara Stoll"; "Ira Adams-Chapman"; "Ellen Hale"
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: SUPPORT
Date: Tuesday, July 29, 2008 10:52:01 AM

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER	NETWORK	FU_message
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Tuesday, July 29, 2008 10:50:54 AM

Hi,
We are missing a few primary outcomes for SUPPORT. Let us know how you are doing. Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
8	(b) (6)	The patient's follow-up window has closed and final ROP status has not been reported.
8	[redacted]	The patient's follow-up window has closed and final ROP status has not been reported.
8	[redacted]	The patient's follow-up window has closed and final ROP status has not been reported.
8	[redacted]	The patient's follow-up window has closed and final ROP status has not been reported.

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Newman, Jamie
To: JANET.MORGAN@childrens.com
Cc: Roy.Heyne@UTSouthwestern.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; BVohr@WIHRI.org
Subject: RE: SUPPORT patient with Bayley II rather than III - Ctr 4 Dallas
Date: Monday, July 28, 2008 10:57:41 AM

Janet,
Marie re-ran the report listing SUPPORT infants that have a Bayley 2 at follow-up on July 25 and an additional infant (Network #(b) (6)) showed up this time. We had already discussed infant (b) (6) in March.

Center ID number	Network number	FU Center	Follow Up Number	Delivery Date	Bayley II Date	Bayley II Adjusted Age	MDI	PDI	Bayley III Date	Bayley III Adjusted Age	Bayley III Composite Cognitive Score
4	(b) (6)	4	(b) (6)	(b) (6)	01/25/08	24	72	96	.	.	.

Thanks, Jamie

From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Monday, March 03, 2008 1:46 PM
To: Newman, Jamie; JANET.MORGAN@childrens.com
Cc: Roy.Heyne@UTSouthwestern.edu; higginsr@mail.nih.gov; Das, Abhik
Subject: RE: SUPPORT patient with Bayley II rather than III - Ctr 4 Dallas

Probably correct. Although, we do not know if the MDI was impacted by low language skills.

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, March 03, 2008 1:29 PM
To: JANET.MORGAN@childrens.com
Cc: Roy.Heyne@UTSouthwestern.edu; Betty Vohr; higginsr@mail.nih.gov; Das, Abhik
Subject: SUPPORT patient with Bayley II rather than III - Ctr 4 Dallas

Janet,
Though it would be "nice" to have a Bayley III on the SUPPORT patient below, this infant would classify as impaired for analysis purposes.

Center ID number	Network number	FU Center	Follow Up Number	Delivery Date	Bayley II Date	Bayley II Adjusted Age	MDI	PDI	Bayley III Date	Bayley III Adjusted Age	Bayley III Composite Cognitive Score
4	(b) (6)	4	(b) (6)	(b) (6)	01/25/08	24	58	73	.	.	.

Thanks again for bringing this patient to our attention.
Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Friday, July 25, 2008 9:48:52 AM
Attachments: Infants with missing outcomes 07-24-08.xls

Rose,

Attached is a report of SUPPORT infants missing outcomes this month. The ROP list now includes messages for infants whose follow-up windows are open (or closed) who do not yet have final ROP status.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
8		The patient's follow-up window has closed and final ROP status has not been reported.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
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11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
12		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
12		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 55 weeks PMA has been reached.
14		The patient's follow-up window has closed and final ROP status has not been reported.
15		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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18		The patient's follow-up window has closed and final ROP status has not been reported.
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18		The patient is within their Fol-up window and final ROP status has not been reported.
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18		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
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19		The patient's follow-up window has closed and final ROP status has not been reported.
19		No SUPP10 forms have been entered though 55 weeks PMA has been reached and the infant did not die early.
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24		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Finer, Neil
To: Cunningham, Meg; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Steering Comm newest version
Date: Tuesday, July 22, 2008 10:45:30 AM
Attachments: Steering Committee Report July 22 revised 2008.ppt

---

Meg
If you have time can you load this version for me?
I will be on the phone in 5 minutes waiting
Thanks
Neil

Steering Committee Report
SUPPORT July 22, 2008

Neil Finer – PI for the SUPPORT SubCommittee

Enrollment - Completion

- Enrollment = 1109
- 200 infants to go
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- Should complete by Feb 09, and have final data apart from follow-up about 4 - 6 months later
- Will be too late for PAS –
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- Continuing as expected
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- We ran a baby on Masimo and Nellcor simultaneously – both legs
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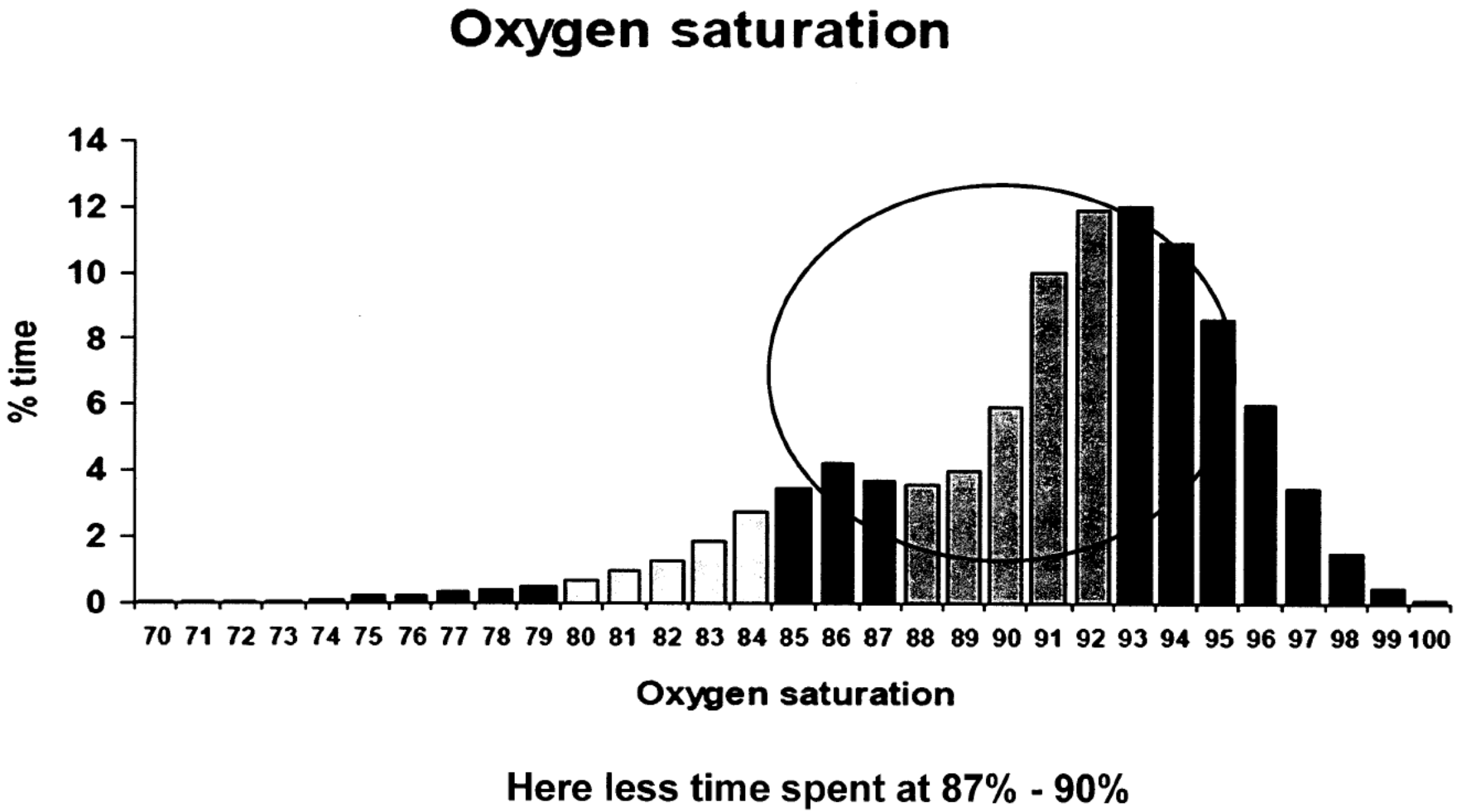

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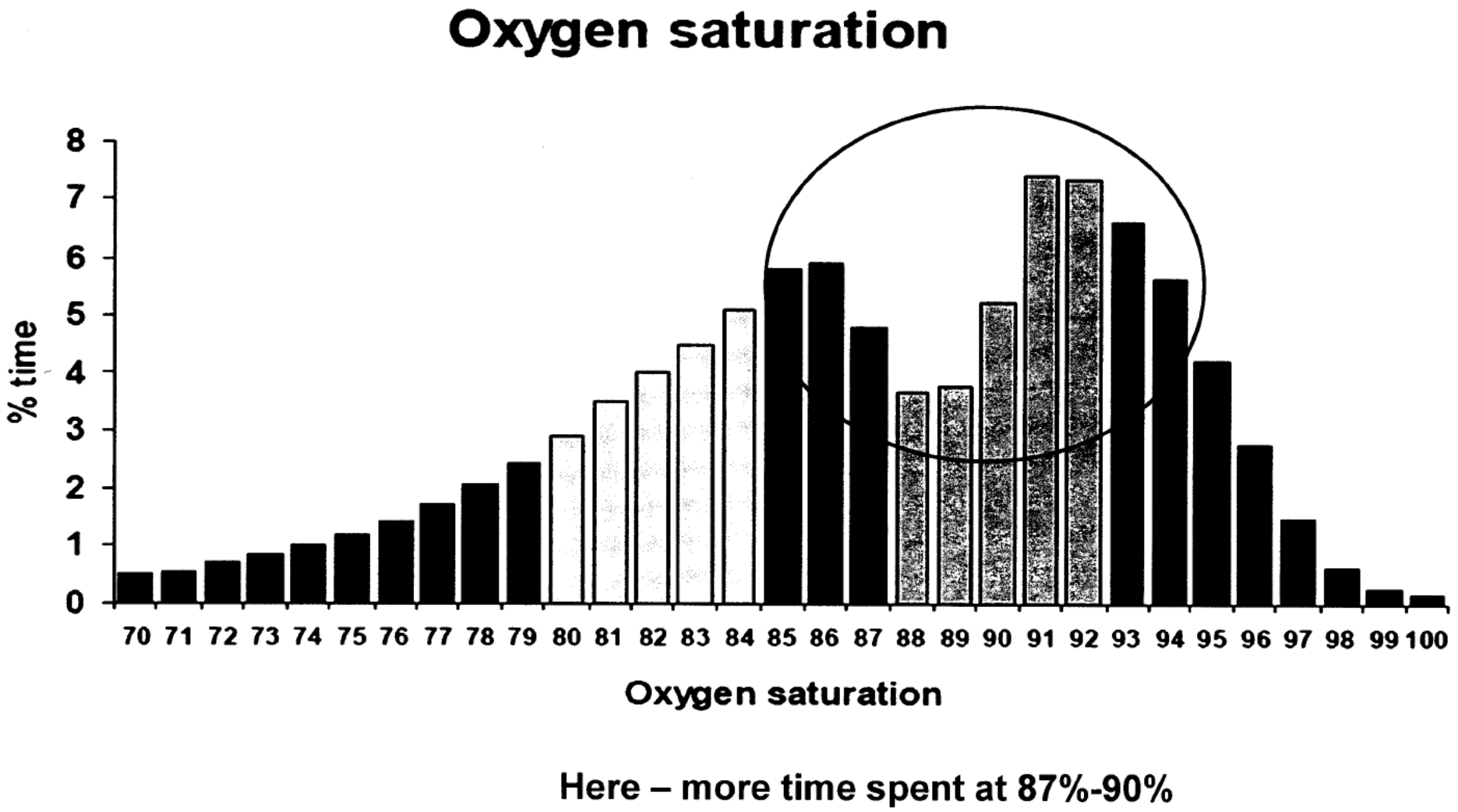

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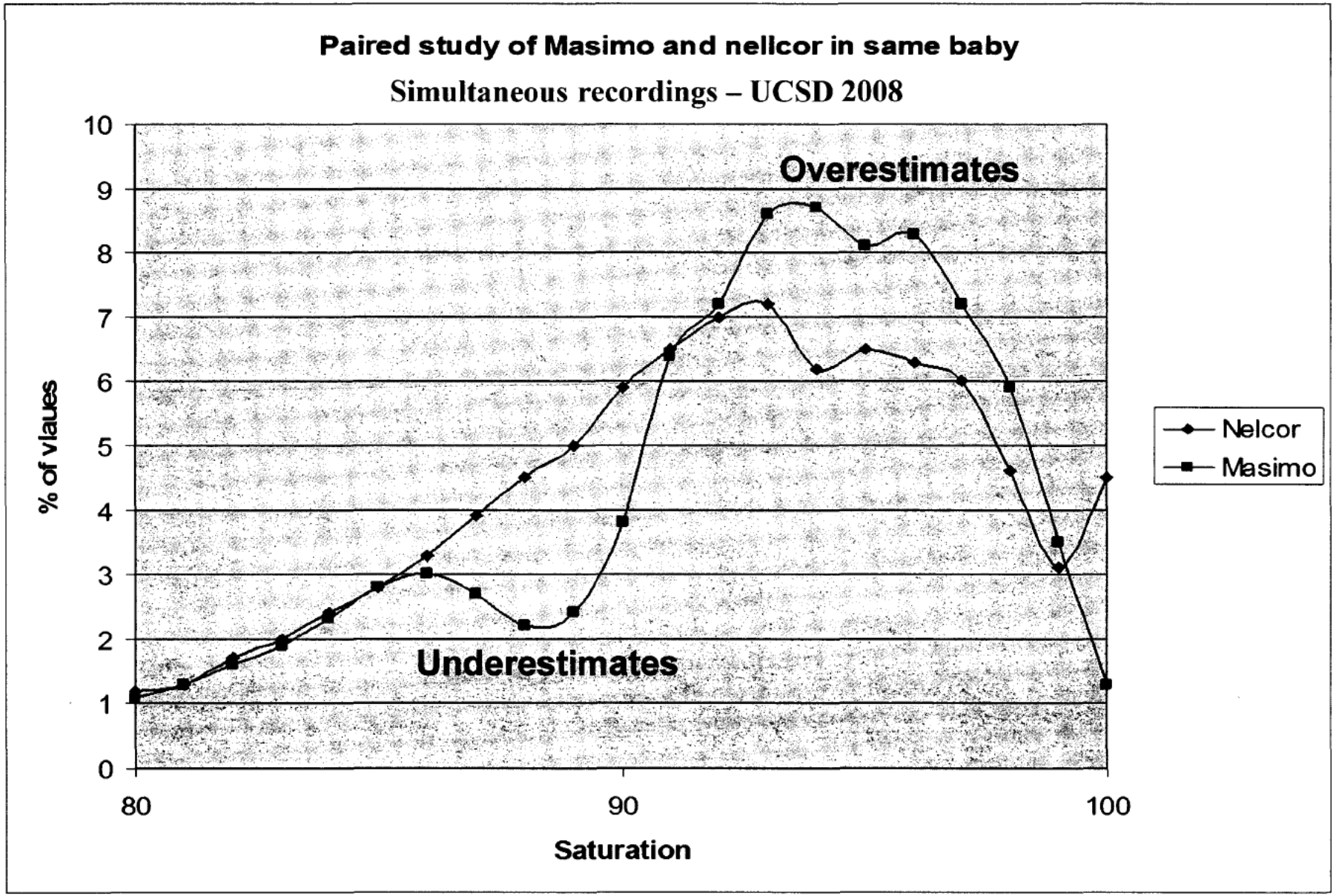
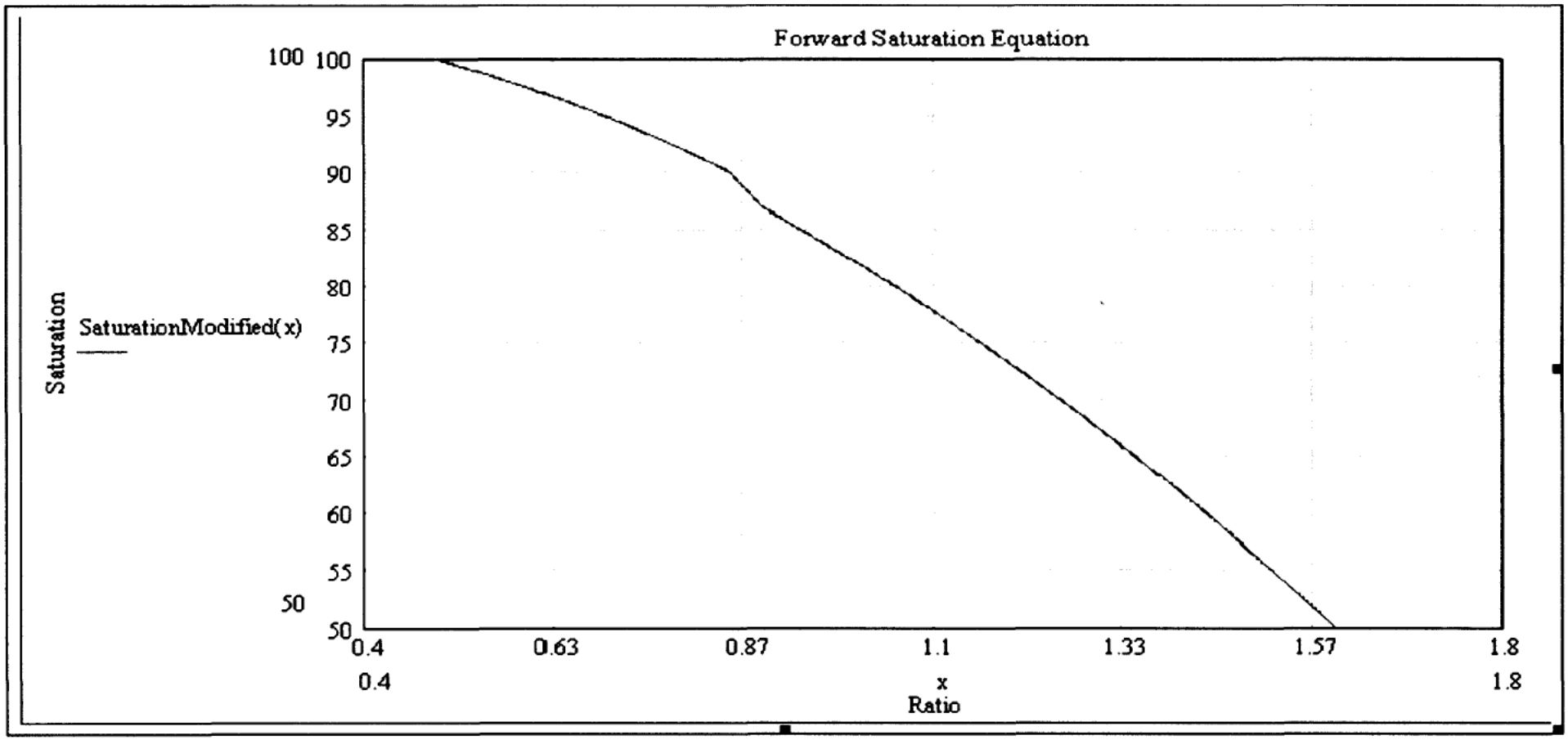
Plot of Cumulative SpO2 from Nellcor (Blue) vs Masimo (Pink) from single baby



Explanation – 2 Curves spliced into one



Answer – Smoothed Curve
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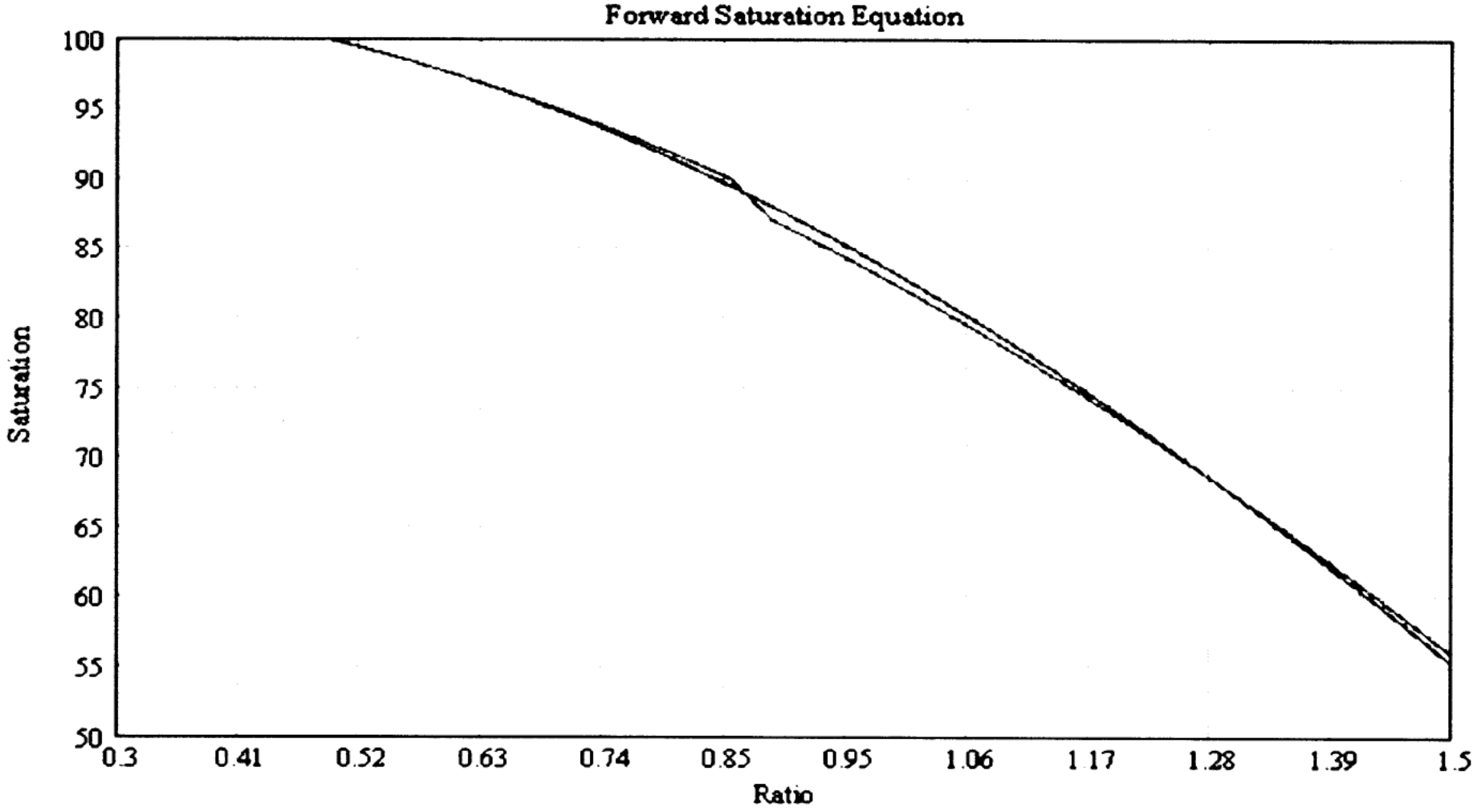

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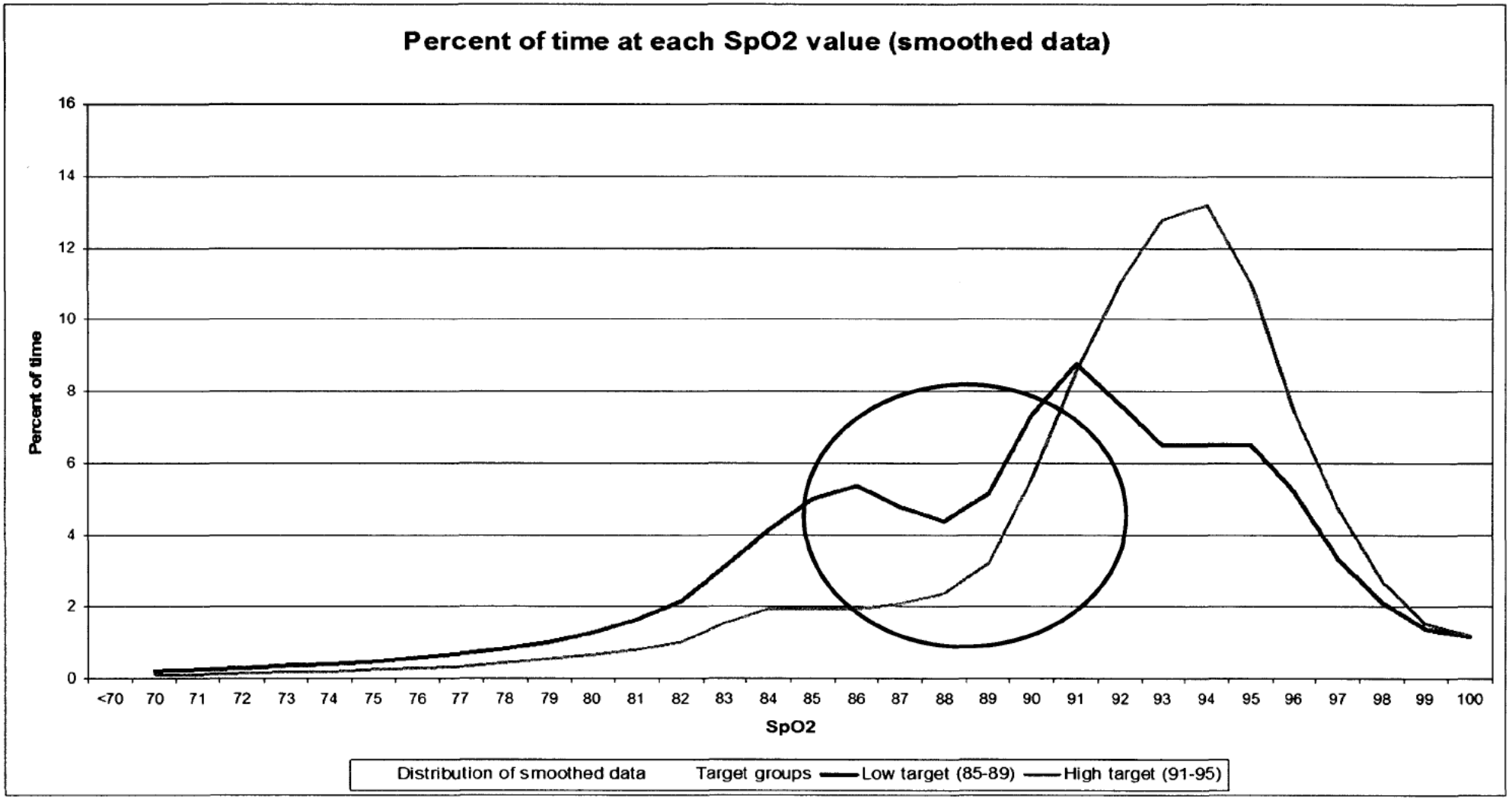
Unblinded Data for DSMC Jan 2005



Response of Dr Avery to Masimo issue

- I agree with continuing. The DSMC felt the study has not achieved the goal of administering oxygen, in the protocol-specified range, to the two groups. Thus a negative final result might be in error. However, if there is a positive result, then a strong enough signal is there to adduce an advantage based on intent to treat. In the real world, intent to treat is what we have. The fact that oxygen sats wander a lot in very sick premies is part of that real world. Best. Gordon

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- I believe that if there is any fault attributable to any investigator – it can only be assigned to me.
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- I did try to get Nellcor to work with us to develop a study oximeter – no interest – (Oh yes, they were being sued by Masimo)
- Here is your chuckle for the day
- The merged 2 curves was so that the Masimo would better resemble the values in the higher SpO2 ranges as reported by the Nellcor!!

- **Thanks to everyone for all the great efforts to get this study done.**

- **Safe travels!**

From: Finer, Neil
To: Cunningham, Meg; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Updated SC Agenda
Date: Tuesday, July 22, 2008 12:38:43 AM
Attachments: Steering Committee Report July 22 2008.ppt

Hi Meg
Can you load this up for my presentation tomorrow at 11:00AM – 8:00AM Pacific Time
I will ask you to advance the slides.
Many thanks
Neil

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Thursday, July 17, 2008 8:00 AM
To: enylen@tuftsmedicalcenter.org; bbillian@wayne.edu; Bethany Ball; Conra Lacy; ellen_hale@oz.ped.emory.edu; Georgia.E.McDavid@uth.tmc.edu; Johnson, Karen; karen.osborne@hsc.utah.edu; ldw@iupui.edu; mcollins@peds.uab.edu; melissa.leps@utsouthwestern.edu; monica.konstantino@yale.edu; nancy newman; Nancy.Miller@UTSouthwestern.edu; rbara@med.wayne.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; David Stevenson; Bradley Yoder; rohls@salud.unm.edu; Sood, Beena; ambal@uab.edu; William Oh; Michael Cotten; benja005@mc.duke.edu; bvohr@wihri.org; Finer, Neil; Rich, Wade; dpcarlt@emory.edu; edward.donovan@cchmc.org; dale_phelps@urmc.rochester.edu
Cc: Monica Bocaner; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; jwaidne@emory.edu; lmoore@med.wayne.edu; jrose@wihri.org; kgilley@wihri.org; Alice.J.Reardon@uth.tmc.edu; Martinez, Fernando; gonza025@mc.duke.edu; msumner@peds.uab.edu; debra.camputaro@yale.edu; Auman, Jeanette O.; Pickett, James; Gantz, Marie; Newman, Jamie; Wrage, Lisa Ann
Subject: Updated SC Agenda

Dear All-

Attached you will find an updated agenda.

Please visit the NRN website to see the concepts that will be presented during the meeting. To access the concepts please follow these links on the NRN website: Protocol Review **>** Concepts **> July 2008**

Lastly, for those that are calling in for concepts or subcommittee meetings please call:
Outside the USA : **1-203-310**(b) (6)
Within the USA : **866-675**(b) (6)
Then, enter Participant Passcode: (b) (6) **#**
******Please inform me what you are calling in for prior to the meeting so the line can be opened.***

Looking forward to seeing you all soon!
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837

fax: 202-728-2095
www.rti.org

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SUPPORT July 22, 2008

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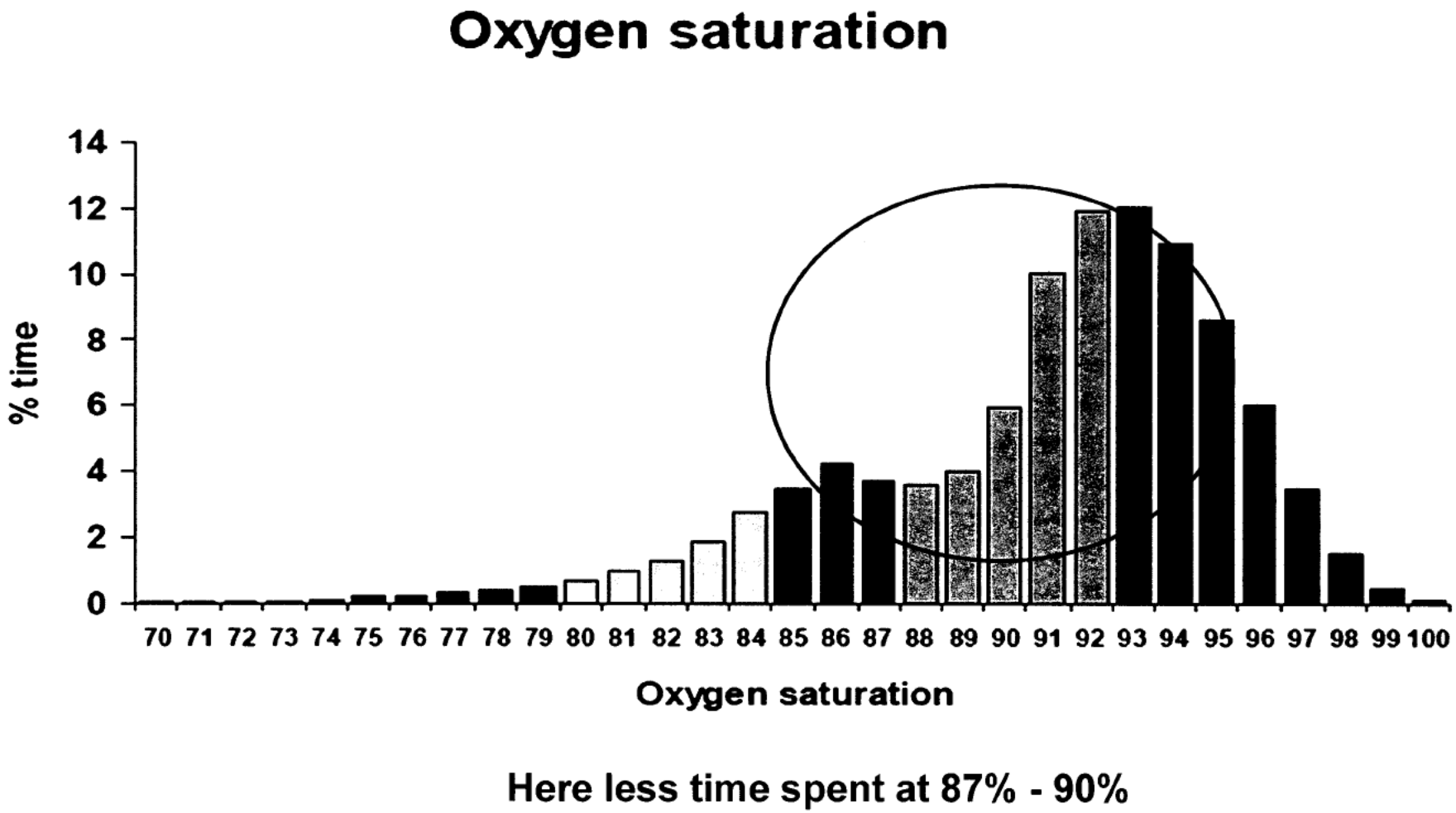

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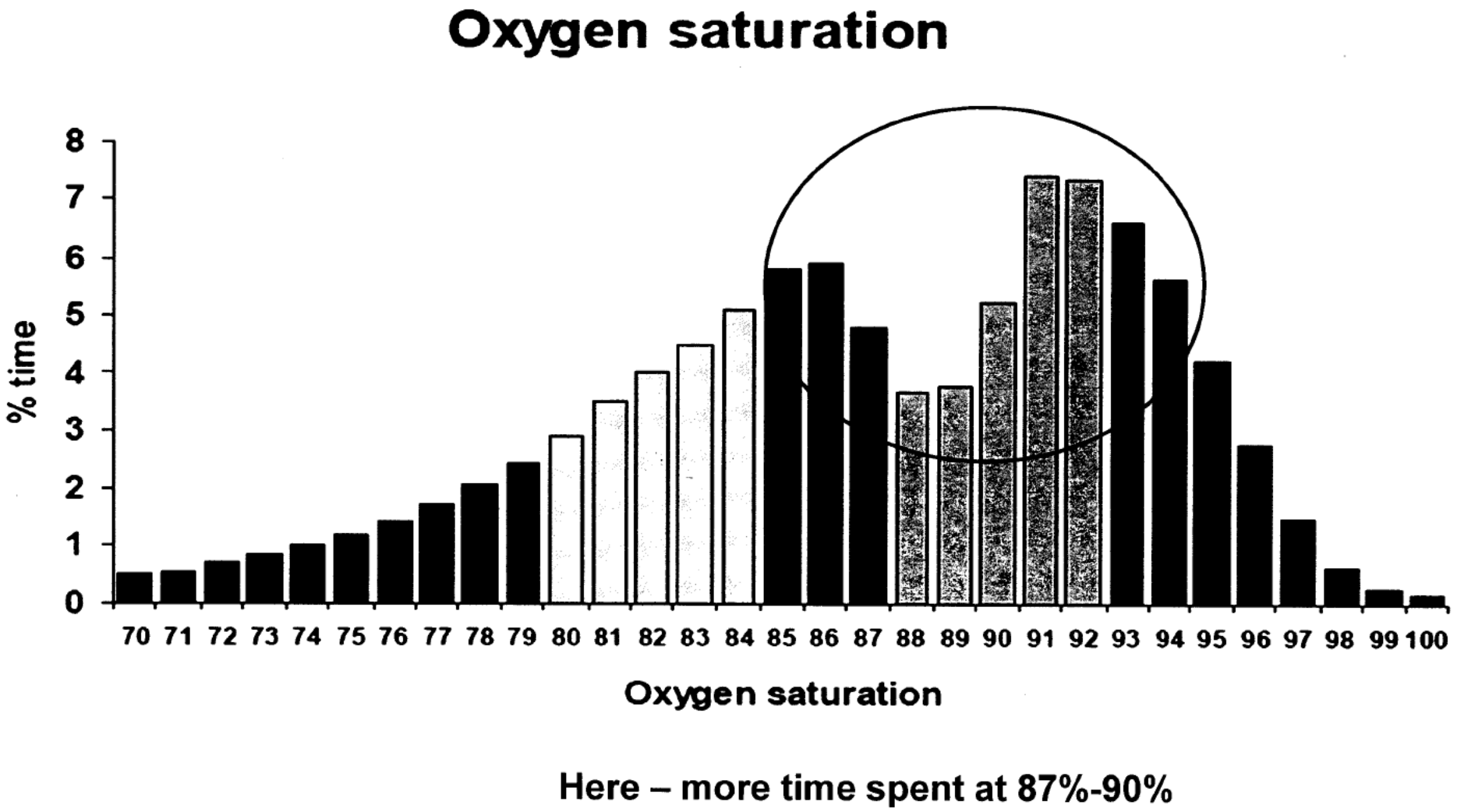

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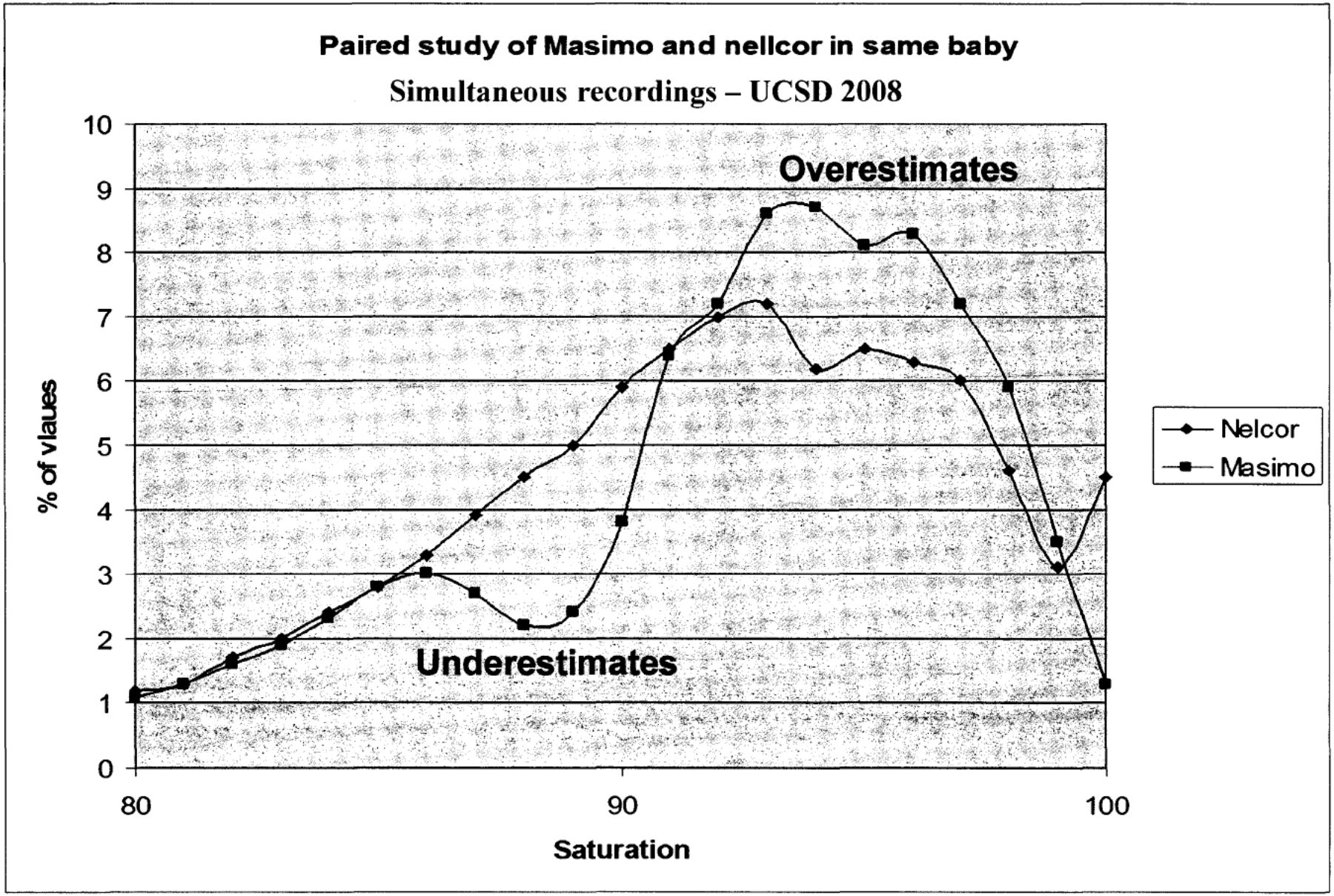

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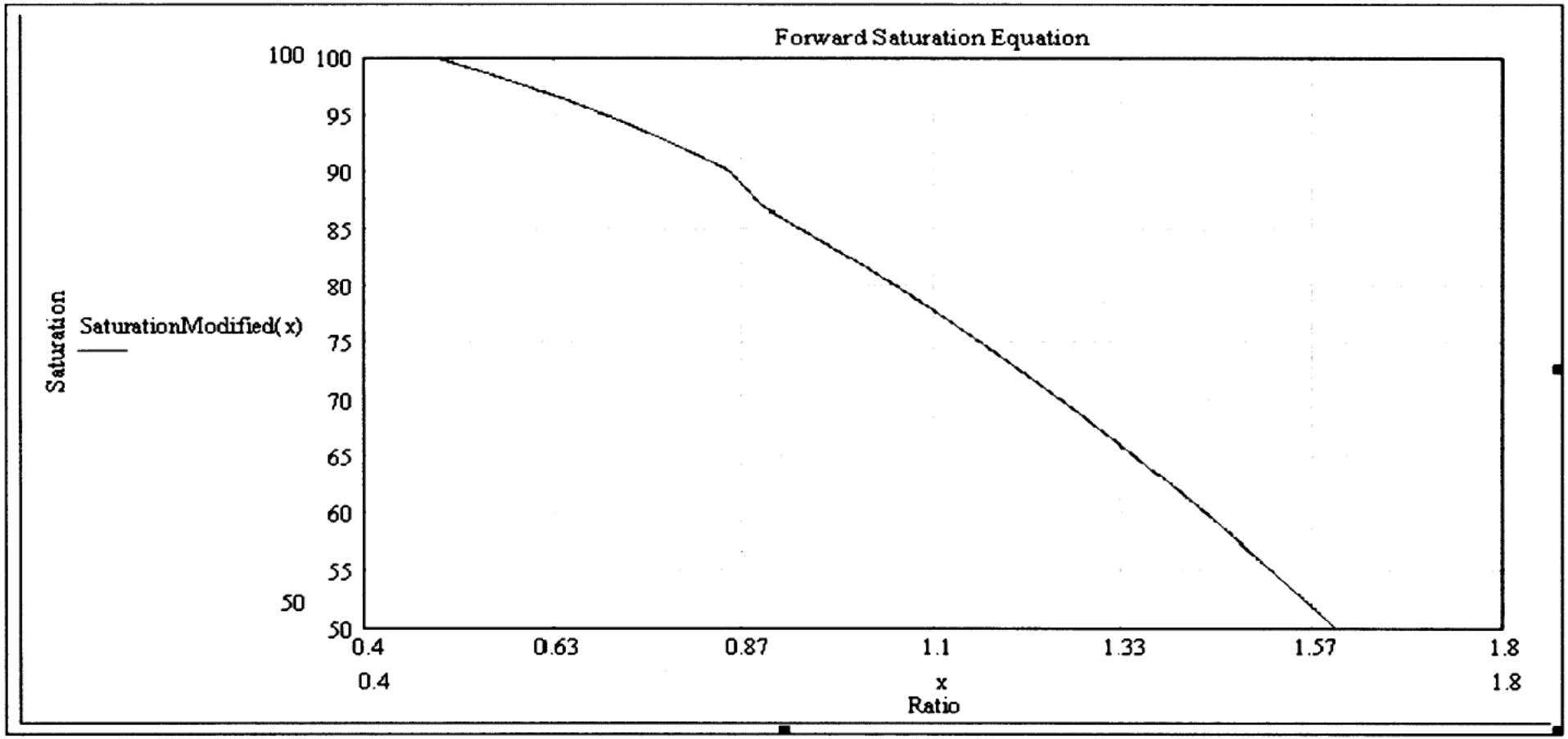

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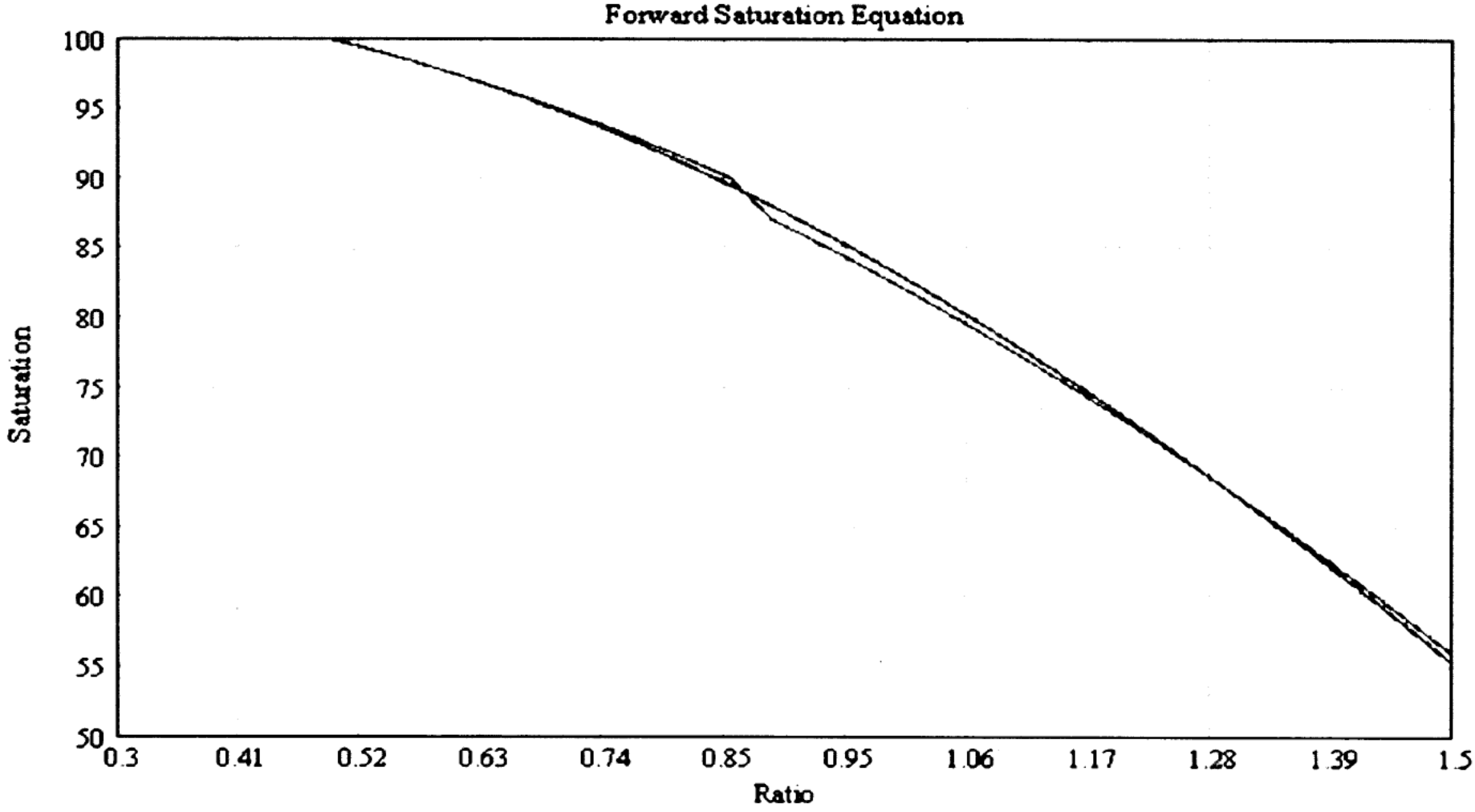

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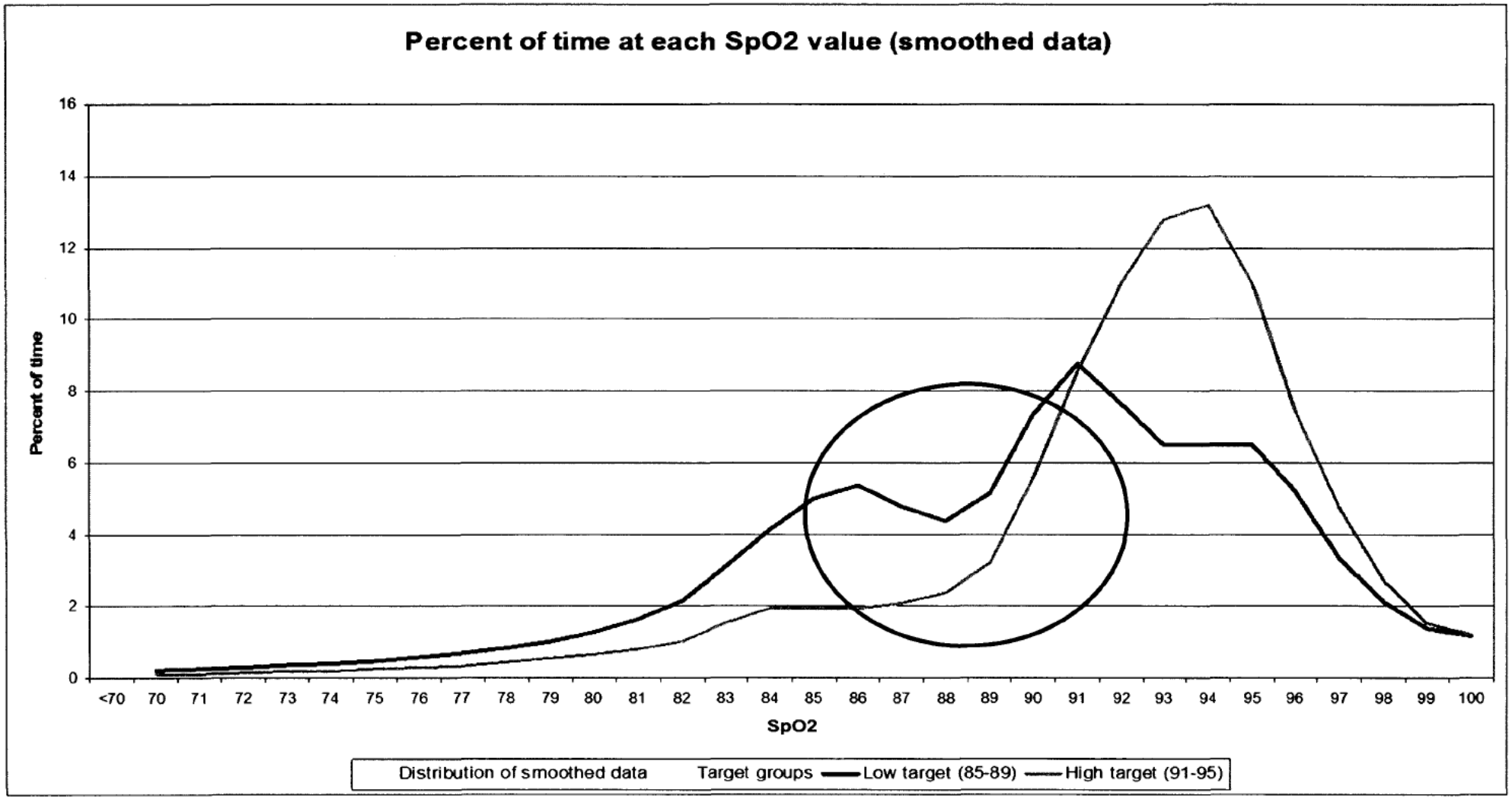

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From: Cunningham, Meg
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT and Probiotics materials
Date: Friday, July 18, 2008 5:46:24 PM

We can have Monica copy stuff at the Bolger too!

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Friday, July 18, 2008 5:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: SUPPORT and Probiotics materials

We owe Susan! Nichole and Tamika are already gone for the day, and I have to (b) (6) . Susan's here late, so she's going to copy these and bring the over on Monday.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 18, 2008 4:14 PM
To: 'mcunningham@rti.org'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw:

For SUPPORT

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Jul 18 14:52:41 2008
Subject: FW:

Rose

Do you want a lot of information sent to the Steering Comm - ie Protocol violations etc?

I can just give the report and talk about the Masimo issue.

Let me know

Neil

Neil N. Finer, M.D.

Professor of Pediatrics

Director, Division of Neonatal-Perinatal Medicine

UC San Diego School of Medicine

UC San Diego Medical Center, Hillcrest

402 Dickinson St., MPF 1-140

San Diego, CA 92103-8774

Telephone: 619.543-3759

Facsimile: 619.543.3812

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, July 16, 2008 3:31 PM
To: Finer, Neil
Cc: Das, Abhik
Subject:

Neil,

Attached are SUPPORT updates for the Steering Committee meeting next week. The pulse oximeter data are currently being processed, but I aim to have those reports to you by the end of the week.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Gordon Avery
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Massimo oximeters
Date: Friday, July 18, 2008 8:42:40 AM

I agree with continuing. The DSMC felt the study has not achieved the goal of administering oxygen, in the protocol-specified range, to the two groups. Thus a negative final result might be in error. However, if there is a positive result, then a strong enough signal is there to adduce an advantage based on intent to treat. In the real world, intent to treat is what we have. The fact that oxygen sats wander a lot in very sick premies is part of that real world. Best. Gordon

On Thu, Jul 3, 2008 at 3:06 PM, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov> wrote:

> Dr. Avery,
>
> It has come to the SUPPORT investigators attention that the Massimo oximeters have an inherent software issue whereby the calibration used to convert the wavelength ratios to an SpO2 value via the sensor placed on the baby results in a decreased time at SpO2 between 87-90%. This was identified by investigators performing the other trials around the world including BOOST II, Canadian oxygention trial and the UK oximetry trial. This results in a slight dip in the calibration curve as shown in the first figure on 7.3.08 conf call slide. This is inherent to all Massimo oximeters (not just study oximeters) but is in the area of target for the low saturation group.
>
> The Massimo Company had a conference call with the investigators of the various trials around the world today and sent the attached pdf. In retrospect, this was visible in our low target group (see slide 19 on the attached PowerPoint presentation that Neil Finer presented to the DSMC in January 2006). It is our understanding that the DSMC has evaluated separation of the two groups and time in oxygen and we are to concentrate on obtaining target saturations.
>
> The Massimo company is going to send all of the investigators of the trials a document next week outlining this issue. The SUPPORT subcommittee has discussed the issue as well as the NRN steering committee. Since we have already enrolled almost 1100 children and there have been two looks by the DSMC so far, we think it prudent to continue, unless you see otherwise.
>
> I will forward you additional information as I receive it from Massimo.
>
> Let me know if you agree.
>
> Regards,

From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	FW:
Date:	Friday, July 18, 2008 2:52:24 PM
Attachments:	SUPPORT Enrollment 7-08-08.doc SUPPORT Adverse Events 07-08-08.doc SUPPORT Protocol Deviations - old vs new 07-08-08.doc SUPPORT Protocol Deviations by center - old vs new 07-08-08.doc SUPPORT Use of HFNC 07-08-08.doc Calibration Curve Explanation 07 10 08f.doc Minutes of Meeting with ROP Study Investigators 07 10 08.doc

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Research Statistician
RTI International
mgantz@rti.org
828-254-6255

SUPPORT Enrollment as of July 8, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	1109	85%

Enrollment by Center

Center	<Jan-08	Jan-08	Feb-08	Mar-08	Apr-08	May-08	Jun-08	Jul-08	Total
3	79	2	3	4	1	1	5	0	95
4	46	0	1	7	4	2	1	0	61
5	39	4	1	4	2	2	4	1	57
8	17	0	0	0	0	0	0	0	17
9	59	1	0	3	5	0	1	0	69
11	66	5	1	4	2	4	0	0	82
12	53	2	2	1	1	0	0	1	60
13	21	4	0	0	1	0	2	0	28
14	82	6	2	6	6	5	3	0	110
15	34	0	1	3	1	2	0	0	41
16	124	9	2	8	7	5	4	0	159
18	62	0	1	2	2	2	4	0	73
19	49	2	1	1	0	0	0	0	53
20	9	0	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	0	8
22	56	0	1	1	1	0	0	0	59
23	40	0	1	1	0	0	3	0	45
24	17	1	2	0	1	3	0	0	24
25	29	0	1	4	5	6	0	0	45
26	10	1	0	1	0	0	2	0	14
Total	900	37	20	50	39	32	29	2	1109
Centers		17	17	17	17	17	17	17	
Avg/center		2.2	1.2	2.9	2.3	1.9	1.7	0.1	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	6
2.5	5
3	4

Percent of SUPPORT infants with selected adverse events as of July 8, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.4	9.3	4.2
Air leak (pneumothorax, PIE, pneumopericardium)	9.6	12.6	7.3
Pulmonary hemorrhage	7.0	11.5	3.7
Severe IVH (grades III-IV)	14.3	20.4	9.9

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak (pneumothorax)	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – July 8, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	3
Surfactant not given in the first hour (surfactant group)	26
Surfactant not given in the first hour (CPAP group)	30
Oximeter not started within 2 hours	20
Infant placed on study oximeter for incorrect treatment	13
Failure to use study oximeter at times required by protocol	70
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	22
Randomization/consent errors	24
Other	5
Total	242

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	79
Infant placed on study oximeter for incorrect treatment	13
Failure to use study oximeter at times required by protocol	70
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	9
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	22
Randomization/consent errors	24
Other	5
Total	242

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	0
Surfactant not given in the first hour (surfactant group)	7
Surfactant not given in the first hour (CPAP group)	6
Oximeter not started within 2 hours	7
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	61

Type of protocol deviation (some categories collapsed)	Number
Treatment not implemented within required amount of time	20
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	61

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – July 8, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			1								1	1									3
Surfactant not given in the first hour (surfactant group)	2	4	1			3	1	2	2		3		1					5	2		26
Surfactant not given in the first hour (CPAP group)	3	2				1		1	6	2	4	1	1				1	5	2	1	30
Oximeter not started within 2 hours	1	1	1			1	2			2	2	2	1			1	2	1	3		20
Infant placed on study oximeter for incorrect treatment	3		1			1	1				4		1				1		1		13
Failure to use study oximeter at times required by protocol	2	4	14		2	5	5	1	9		7		2				3	5	8	3	70
Non-study (unmasked) oximeter used at same time as study ox						2	1			1			1						2		7
Mechanical ventilation initiated for other than study criteria																	1				1
NSIMV initiated in infant not previously intubated	1				1						4										6
Extubation (excluding unplanned) for other than study criteria						2			5		2										9
Failure to extubate CPAP infant if all criteria met								1		2											3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1										2
Infant received postnatal steroids in first 21 days of life	1					2		2	5		2	8	1				1				22
Randomization/consent errors	1		4		3	1				3		4	2								24
Other									1	1	2								1		5
Total	14	12	23	0	6	19	10	7	28	11	32	16	10	0	0	2	13	16	19	4	242

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – July 8, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2%								1%	2%									0%
Surfactant not given in the first hour (surfactant group)	3%	8%	2%			5%	2%	7%	2%		2%		3%					21%	4%		3%
Surfactant not given in the first hour (CPAP group)	4%	4%				2%		4%	7%	5%	3%	2%	3%				2%	21%	4%	7%	3%
Oximeter not started within 2 hours	1%	2%	2%			2%	4%			5%	2%	4%	3%			6%	4%	4%	7%		2%
Infant placed on study oximeter for incorrect treatment	4%		2%			2%	2%				3%		3%				2%		2%		2%
Failure to use study oximeter at times required by protocol	3%	8%	25%		4%	8%	10%	4%	10%		6%		5%				7%	21%	18%	21%	8%
Non-study (unmasked) oximeter used at same time as study ox						3%	2%			3%			3%						4%		1%
Mechanical ventilation initiated for other than study criteria																	2%				0%
NSIMV initiated in infant not previously intubated	1%				2%						3%										1%
Extubation (excluding unplanned) for other than study criteria						3%			6%		2%										1%
Failure to extubate CPAP infant if all criteria met								4%		5%											0%
Failure to extubate surfactant infant if all criteria met						2%															0%
Infant intubated without meeting study criteria			2%								1%										0%
Infant received postnatal steroids in first 21 days of life	1%					3%		7%	6%		2%	15%	3%				2%				3%
Randomization/consent errors	1%	2%	7%		5%	2%				8%		7%	5%			6%	9%				2%
Other									1%	3%	2%								2%		1%
Total protocol deviations	20%	24%	40%		11%	30%	20%	26%	32%	28%	26%	30%	26%		0%	11%	29%	67%	42%	29%	28%
Total number of infants enrolled	71	51	57	0	56	63	50	27	88	39	121	54	38	0	1	18	45	24	45	14	862

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0
Surfactant not given in the first hour (surfactant group)	2			1		2	1				1										7
Surfactant not given in the first hour (CPAP group)	4			2																	6
Oximeter not started within 2 hours						1					5	1									7
Infant placed on study oximeter for incorrect treatment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox.															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1												2							3
Other						1					1										2
Total	9	4	0	4	0	7	1	0	4	0	16	2	1	3	3	7	0	0	0	0	61

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol																					0%
Surfactant not given in the first hour (surfactant group)	8%			6%		11%	10%				3%										3%
Surfactant not given in the first hour (CPAP group)	17%			12%																	2%
Oximeter not started within 2 hours						5%					13%	5%									3%
Infant placed on study oximeter for incorrect treatment	4%			6%							11%					2%					3%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						6%
Non-study (unmasked) oximeter used at same time as study ox.															14%						0%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	38%	40%		24%	0%	37%	10%	0%	18%	0%	42%	11%	7%	33%	43%	17%					25%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of July 8, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			3	4%
4			10	20%
5			8	14%
9			12	21%
11	1	5%	6	10%
12			9	18%
13			4	15%
14	1	5%	6	7%
15			1	3%
16			3	2%
18	1	5%	7	13%
19			9	24%
22			1	6%
23			1	2%
24			1	4%
25			7	16%
Total	3	1%	88	10%

Masimo's Neonatal Calibration Curve

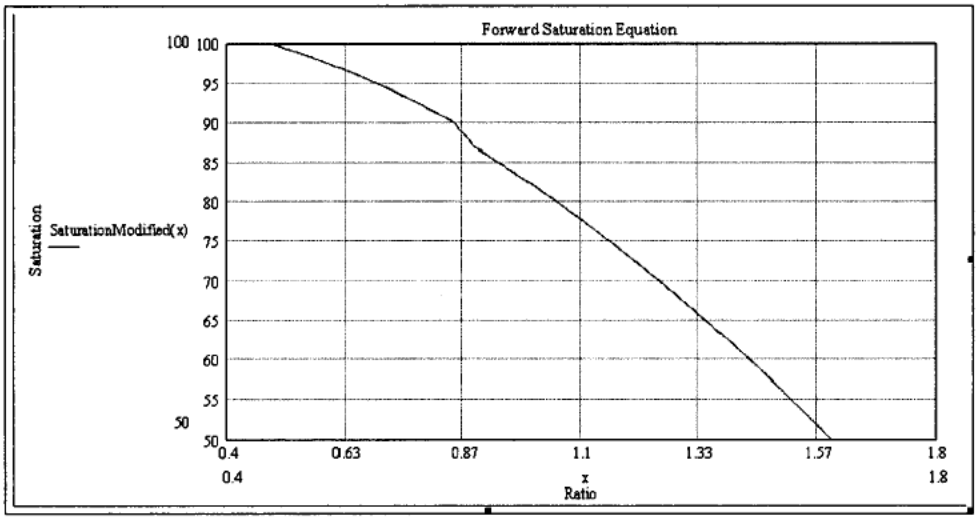
Summary

In 2002, Masimo SET joined two calibration curves to balance what clinicians were accustomed to seeing and to achieve the most accurate, reliable and clinically relevant data for neonates in the critical range. The transition area where the two calibration curves are joined occurs between 87% and 90% saturation. Although the slope of the calibration curve is steeper at this transition it does not affect the accuracy of the device.

The Current Neonatal Calibration Curve

Pulse oximeters are empirically calibrated on normal, healthy adult volunteers during desaturation studies. Because many clinicians over the years have expressed a preference to see a display of 100% SpO_2 when a patient is being treated with 100% oxygen, early pulse oximetry manufacturers adjusted their calibration equation to obviate the effects of the low circulating levels of variant hemoglobins that cause the device to read slightly lower. The calibration adjustment for slight over-reading of SpO_2 values is not generally clinically relevant in adult patients with SpO_2 values above 90%. In neonates, however, oxygen saturations need to be closely tracked and the difference between an SpO_2 of 85% and 82% could be of clinical importance. For this reason Masimo SET employs a second calibration curve for neonates which is used when SpO_2 values are 87% or below. The transition area between the two curves (the curve that slightly over-reads when SpO_2 levels are above 90%, and the curve that does not over-read when SpO_2 levels are 87% or lower) occurs from 90-87%. As can be seen in **Figure 1**, the slope of the curve is steeper in the transition area between 87- 90% SpO_2. This means that, statistically, the likelihood that the pulse oximeter will display a value within this range could be slightly reduced and the likelihood of the oximeter displaying values directly adjacent to the transition area may be slightly increased. For this reason when a histogram is plotted from a large data set of pulse oximetry readings, there may be fewer values within this small transition range resulting in a "dip" in the histogram.

Figure 1. Current Calibration Curve.

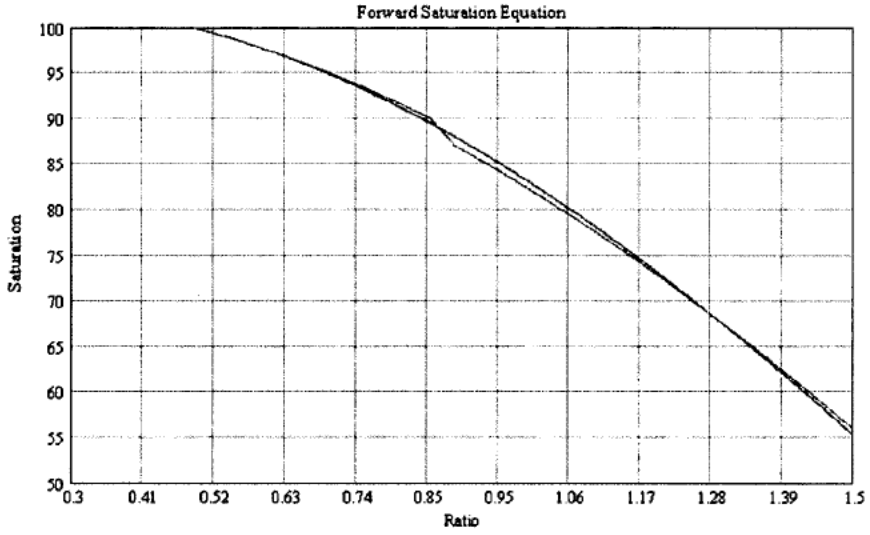


Plot of the ratio of red to infrared wavelength intensities and corresponding oxygen saturations for the current calibration curve.

A Smooth Calibration Curve

All Masimo pulse oximeters perform within specifications. Masimo has, however created a new "smooth calibration curve" in response to observations by the ROP investigators. This smooth curve is a mathematical adjustment of the existing curve. The new calibration curve algorithm essentially smoothes the transition area over a larger range of saturation points diminishing the effect of the transition on any individual saturation value. The current and the smooth calibration curve are depicted in **Figure 2**. In the figure, the current calibration curve is depicted in red and the smooth calibration curve is in blue.

Figure 2. Comparison of the Smooth and Current Calibration Curve.



Plot of the ratio of red to infrared wavelength intensities and corresponding oxygen saturations for the current calibration curve (red) and smooth calibration curve (blue).

The Current Calibration and Smooth Calibration are Both Accurate

The stated accuracy of Masimo pulse oximeters in neonates is +/- 3% at one standard deviation. The actual accuracy however is closer to +/-2%. This is true for devices using the current calibration curve and for any devices that adopt the smooth calibration. **Table 1** shows the probabilities for each saturation point within the transition area of the calibration curve. The shaded column on the graph represents the smooth curve. The statistical probabilities of saturation values within the transition area are slightly lower when calculated from the current calibration curve compared to the smooth curve. For example, the probability of a saturation reading of 88% being within three points is 82% when calculated from the current calibration curve and 87% when calculated from the smooth calibration curve. It is important to note that the probability that an SpO_2 value will be within 3% of the displayed reading is significantly higher from both curves than the stated accuracy of 68%.

Table 1. Probability Table for a Pulse Oximeter with an Accuracy Specification of +/-2%

PROBABILITY									
SpO_2 Value	Smooth Curve @ any SpO_2 value	Piece wise Curve @ SpO_2 = 91 %	Piece wise Curve @ SpO_2 = 90 %	Piece wise Curve @ SpO_2 = 89 %	Piece wise Curve @ SpO_2 = 88 %	Piece wise Curve @ SpO_2 = 87 %	Piece wise Curve @ SpO_2 = 86 %	Piece wise Curve @ SpO_2 = 85 %	Piece wise Curve @ SpO_2 = 84 %
to be within ± 1 %	38	38	37	38	35	35	35	35	35
to be within ± 2 %	68	67	67	68	63	63	63	64	64
to be within ± 3 %	87	86	86	87	82	82	83	83	83
to be within ± 4 %	95	95	95	95	93	93	93	93	94
to be within ± 5 %	99	99	99	99	98	98	98	98	98

Table of the probabilities of SpO_2 values being within a given percent for the smooth calibration (shaded region) and the current calibration.

The Dip in the Histogram Does Not Occur with the Smooth Calibration

If it is the investigators preference to perform a retrospective data analysis with the smooth calibration curve Masimo can provide software for this purpose. If implemented, previously collected data can be reanalyzed with the smooth algorithm. Additionally, the smooth calibration curve can be downloaded (with a serial cable and a laptop computer) into the masked pulse oximeters being used in the ROP trials so that all future data collection will be performed with the smooth curve. Patient data from one of the UK studies was analyzed with the current calibration curve algorithm and the smooth curve algorithm to create the histograms in **Figures 3a, 3b.** In these figures, the red bars represent the data from the existing calibration curve. The blue line represents how the distribution would look if it had been collected with the smooth curve. The black line represents how the distribution would look if data collected with the current calibration were retrospectively analyzed with the smooth curve. The black line will not be identical to the blue line because the processed data exists as full integers whereas data collected with the smooth curve has an additional significant digit.

Figure 3: Saturation Frequencies for High and Low Managed Populations.

Figure 3a.

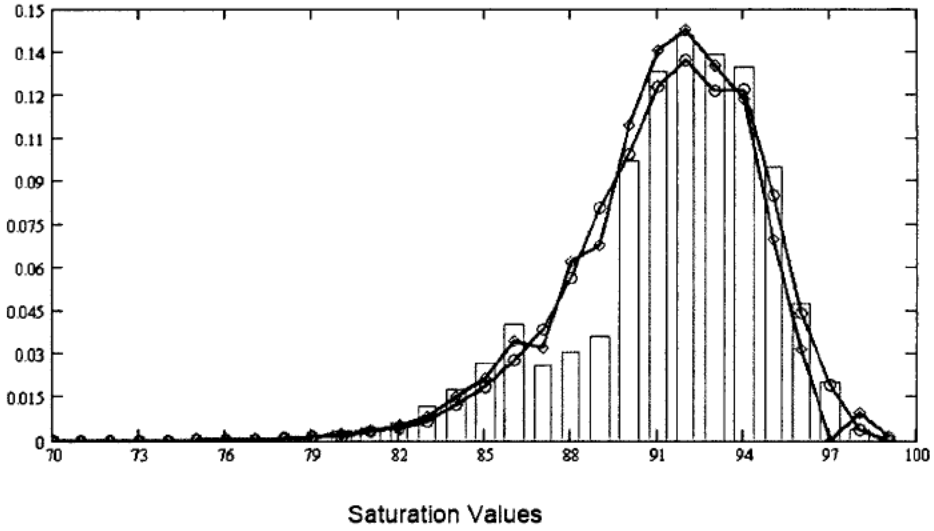
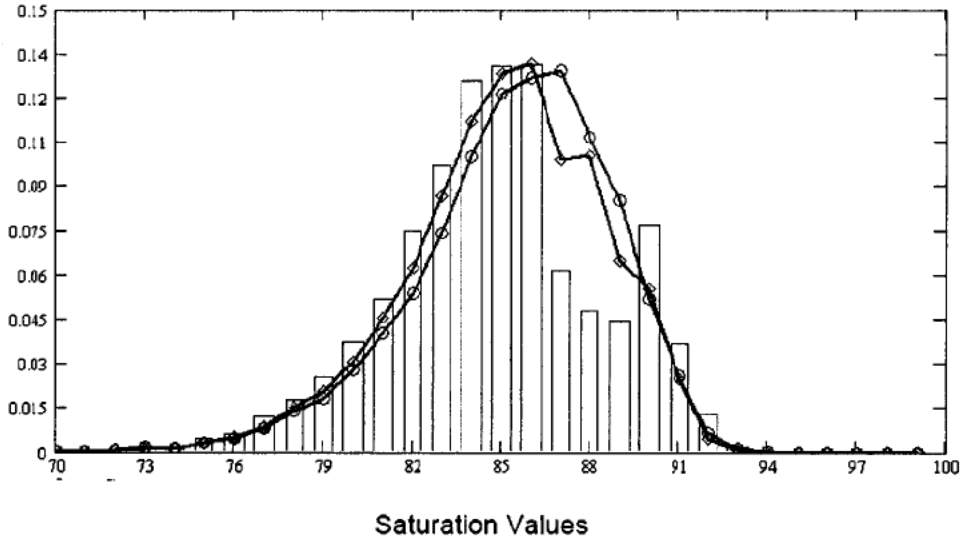


Figure 3b

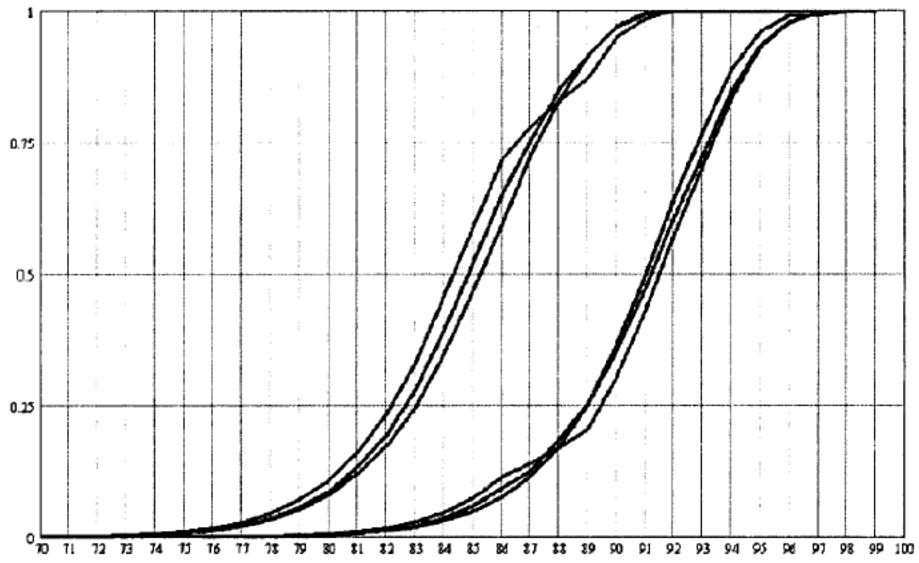


Histogram plot of the saturation values from a population "managed high"(3a) , or "managed low" (3b) collected with the current calibration (red bars) and line plots of the same data reanalyzed with the smooth calibration (black line) and same data collected with the smooth calibration (blue line).

Both the Existing Calibration and the Smooth Calibration Allow for Separation of Saturation Ranges between Groups

Some of the ROP investigators have expressed concerned that the effect of current calibration may mean that it is more difficult to maintain a difference of 6% SpO_2 between the population of patients managed high and the population of patients managed low. **Figure 5** shows the cumulative distribution of saturations for the low managed group (left three curves) and the high managed group (right three curves).

Figure 4: Cumulative Distribution of High and Low Managed Populations.

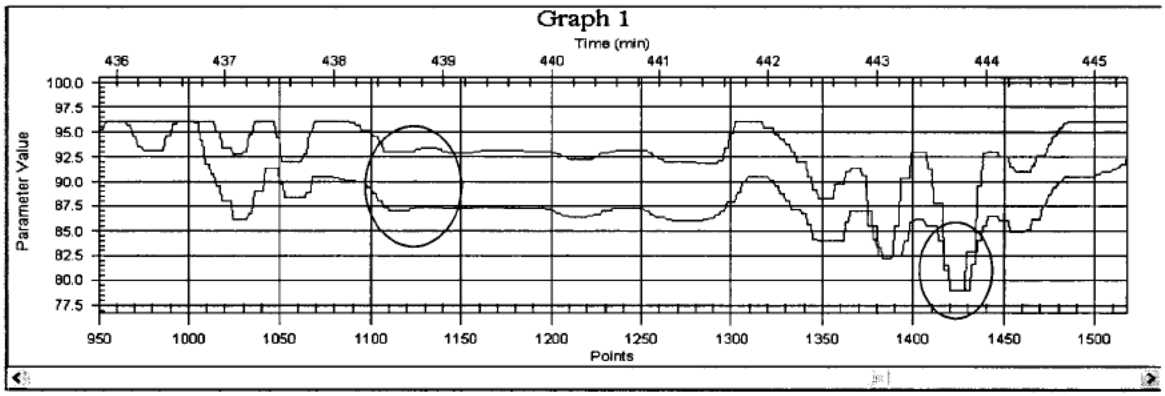


Cumulative distribution plot of the probability of oxygen saturation readings occurring when data is collected from the low managed population (left three curves) or from the high managed population (right three curves) with the current algorithm (red) the smooth algorithm (blue) or reanalyzed with the smooth algorithm (black).

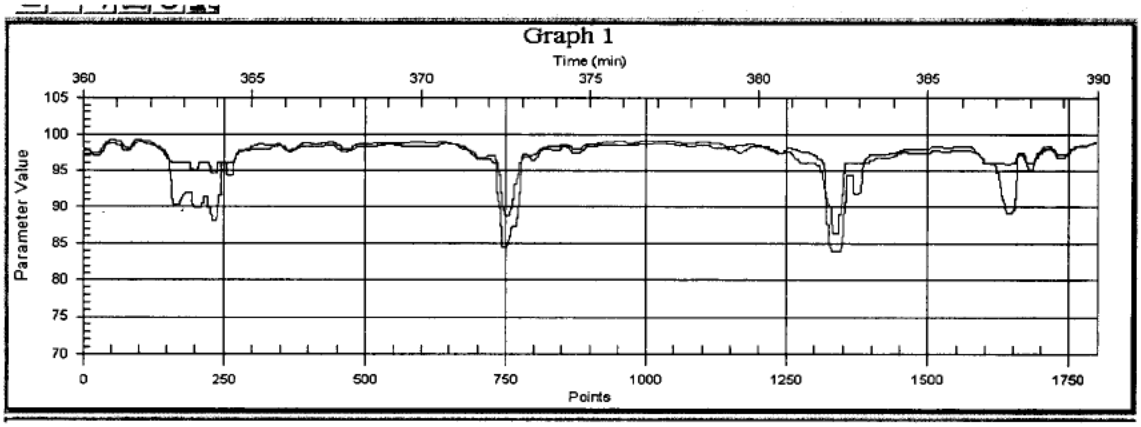
At the 0.5 mark on the Y axis, which represents the center of the population, there is at least a 6% separation in the saturation values between the groups. For the data analyzed with the smooth calibration there is 6% separation between the two groups, whereas for the distribution calculated from the current calibration (red lines), there is slightly more than 6% separation between the two groups. The separation of saturations ranges may be more clearly visualized when one examines data from a single patient that was monitored with both a "high group" device and a "low group" device simultaneously. **Figure 5a and 5b** show the data from one such patient. **Figure 5a** demonstrates that there is between 4-6% difference in the saturation readings between the two

devices when the patient's saturation is between 87 and 95%. At the lower range, below 85%, the saturations displayed by the two devices transition back together and read the same. Likewise, **Figure 5b** shows that the two devices read the same when the patient's saturation is above 95%. There is a clear separation of readings between the two oximeters in the middle range and no separation at the high and low range of saturations, as anticipated by the protocol.

Figure 5: Physiolog Plot of Patient Monitored with High and Low Offset Oximeters



5a. Data from a "high group" (red) oximeter and a "low group" oximeter (blue) reading from one patient, shows the separation of readings of approximately 6% when the patient is between 85- 95% (red circle), with smaller or no separation of the data when the patient is below 84% SpO2 (blue circle).



5b. Data from a "high group" (red) oximeter and a "low group" oximeter (blue) reading from one patient, shows no separation of the data when the patient is above 95% SpO_2.

Minutes from Call with ROP Study Investigators
July 3, 2008; 9:00 AM PST

Participating on the call:
Peter Brocklehurst
Neil Finer
Maria Gantz
Rosemary Higgins
Christian Poets
Jack Rabi
Wade Rich
Barbara Schmidt
Ben Stenson
William Tarnow-Mordo
Robin Whyte

From Masimo:
Ammar Al-Ali
Valerie Begnoche; taking minutes.
Michael O'Reilly

Minutes:

1. Description of the current calibration curve and the potential impact of a smooth calibration curve, including the probability and distribution of saturation values in neonatal patients. Discussion on the effect of a smooth calibration curve on the distribution of saturation values for future data collection and for retrospective reanalysis of data. (See attached).

2. Discussion of the impact of the current calibration curve on the ability to achieve separation in saturation values for the managed high and the managed low populations in the ROP trials.
    a. Study sites are having different degrees of success in achieving separation of values between the two patient groups.
    b. Factors other than the calibration curve, such as the study design or compliance, could be contributing to the ability to achieve separation between groups of patients.
    c. The reasons why certain sites are having difficulty in maintaining 6% separation of saturation values in the middle range between groups of patients remains undetermined.

3. Discussion on the development of a calibration curve for neonates and the impact of varying levels of fetal hemoglobin in these patients.
    a. (b) (4) [redacted]

b. Possibility of improving the accuracy of pulse oximetry with the use of newer more accurate blood gas machines.

4. Discussion regarding what next steps should be for each study group and the reporting to safety monitoring committees.

5. Masimo agrees to provide meeting minutes and an explanation of the current calibration curve to meeting participants.

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Finer, Neil
To: Cunningham, Meg
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Updated SC Agenda
Date: Thursday, July 17, 2008 2:47:37 PM

Hi Meg
I am assuming that we already had the SUPPORT Committee meetings by phone as there is no slot for SUPPORT. That is OK – I just wanted to be sure that this is the plan.
I am getting emails from the Secondary PIs that think that they are required to present – ie Susan and Tim
Neil

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Thursday, July 17, 2008 8:00 AM
To: enylen@tuftsmedicalcenter.org; bbillian@wayne.edu; Bethany Ball; Conra Lacy; ellen_hale@oz.ped.emory.edu; Georgia.E.McDavid@uth.tmc.edu; Johnson, Karen; karen.osborne@hsc.utah.edu; ldw@iupui.edu; mcollins@peds.uab.edu; melissa.leps@utsouthwestern.edu; monica.konstantino@yale.edu; nancy newman; Nancy.Miller@UTSouthwestern.edu; rbara@med.wayne.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; mca113@northwestern.edu; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; David Stevenson; Bradley Yoder; rohls@salud.unm.edu; Sood, Beena; ambal@uab.edu; William Oh; Michael Cotten; benja005@mc.duke.edu; bvohr@wihri.org; Finer, Neil; Rich, Wade; dpcarlt@emory.edu; edward.donovan@cchmc.org; dale_phelps@urmc.rochester.edu
Cc: Monica Bocaner; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; jwaidne@emory.edu; lmoore@med.wayne.edu; jrose@wihri.org; kgilley@wihri.org; Alice.J.Reardon@uth.tmc.edu; Martinez, Fernando; gonza025@mc.duke.edu; msumner@peds.uab.edu; debra.camputaro@yale.edu; Auman, Jeanette O.; Pickett, James; Gantz, Marie; Newman, Jamie; Wrage, Lisa Ann
Subject: Updated SC Agenda

Dear All-

Attached you will find an updated agenda.

Please visit the NRN website to see the concepts that will be presented during the meeting. To access the concepts please follow these links on the NRN website: Protocol Review **>** Concepts **> July 2008**

Lastly, for those that are calling in for concepts or subcommittee meetings please call:
Outside the USA : **1-203-310**(b) (6)
Within the USA : **866-675**(b) (6)
Then, enter Participant Passcode: (b) (6)
******Please inform me what you are calling in for prior to the meeting so the line can be opened.***

Looking forward to seeing you all soon!
Meg

Meg Cunningham
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005

tel: 202-974-7837
fax: 202-728-2095
www.rti.org

From: Susan Hintz
To: neil finer
Cc: vanmeurs@stanford.edu; dstevenson@stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: July SUPPORT Neuroimaging update
Date: Wednesday, July 16, 2008 1:46:40 PM
Attachments: July2008SUPPORTNeuroUpdateHINTZ.doc
SRH_MRI tracking_to_July08.doc

Hi Neil,

Attached is the update for the July Network meeting. I will be a disembodied voice on the phone - on service in the NICU.I also attached my "extra information" sheet for your interest - it gives a breakdown of the reasons why patients did not get MRI's. The most common reason for enrolled but no MRI remains the same - the patient died prior to the window.

As of 6/30/08, there are **347** patients with complete neuroimaging including MRI. An additional 31 are "in the pipeline" - not yet reached their windows or the forms have not yet been completed. The really great news is that the # of patients has increased by ~100 over the past 6 months. So, if we estimate that SUPPORT enrollment will probably be open another 5-6 months, I suspect we will get to at least 450. That is really fantastic.

Only 4.9% of the patients who got MRI's required more than one attempt, and only 8.9% of the patients received sedation (which is steady).

As you know, the "final" vote (priority/budget) is in process for the 6-7 year follow-up proposal.

Hope all is going well for you - I will speak with you soon

Susan

--

Susan R. Hintz, M.D., M.S. Epi
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Division of Neonatal and Developmental Medicine
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Palo Alto, CA 94304
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fax: 650-725-8351

1) Enrollment/Process update

- 15 sites enrolling; data through 6/30/2008
  - **469 patients** have been enrolled in the SUPPORT Neuroimaging secondary
    - **~347 patients** have complete 35-42 week imaging *including MRI*
      - **Of the 122 patients enrolled without MRI:**
        - 69 patients died before MRI
        - 31 with MRI01 not yet complete or window for MRI not reached
        - 22 with other issues including technical/availability (4), attempted but movement or uncooperative (5), patient discharged or transferred prior to MRI (3), clinically unstable (2), other (8)
- MRI central reading –
  - Rolling central reading for SUPPORT MRI's is on hold while Hypothermia MRI's are in process

2) Tracking enrollment

- THANK YOU to all the coordinators who continue to key the first part of the MRI01 form as soon as they can.

3) PROPOSED Extended Follow-up at 6-7 years for SUPPORT Neuroimaging cohort

- Favorable scientific vote (vote #1) by Steering Committee
- Priority vote (vote #2) in process

4) Please call or email with questions, comments, and suggestions

Susan Hintz
650-723-5711 (office)
Email: srhintz@stanford.edu

THANKS TO ALL THE SITES FOR THE HARD WORK ON THIS STUDY!

MRI tracking through 6/30/2008 (for July 2008 Steering Committee)

469 enrolled in SUPPORT Neuroimaging study

347 with MRI COMPLETE

469-347 = 122 patients enrolled that do not have MRI = "incomplete":

Of 122 incomplete:

69 died prior to reaching 35-42 week window

31 with MRI 01 not yet complete – window not yet reached or form not yet keyed

22 with "other issues"

- 1 "site not ready for MRI"
- 3 with "PDA clip in place"
- 4 withdrew consent
- 1 "patient no longer enrolled in study"
- 3 "technical/MRI availability problems"
- 4 "attempted, but unsuccessful due to movement"
- 1 patient uncooperative and mom requested stop MRI
- 1 attending discharged pt and cancelled MRI
- 2 patient transferred before MRI window
- 1 clinically unstable "spits up too much", not attempted
- 1 "on nasal simv can't take patient in the magnet"

From: Karen Osborne RN
To: Archer, Stephanie (NIH/NICHD) [E]; Bradley Yoder
Cc: Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial
Date: Monday, July 14, 2008 4:21:30 PM

Thanks for the explanation Stephanie. I'm sure you're working as fast as you can with this mammoth task and appreciate your efforts!

Karen

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, July 14, 2008 2:13 PM
To: Bradley Yoder; Karen Osborne RN
Cc: Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

HI Karen, Roger, and Brad,

We do not have records of all NRN studies in ClinicalTrials.gov yet, but we do have the ongoing interventional studies, which are the most important and required. I am in the process of updating all of the existing records for NRN, and creating records for the new upcoming study(ies) (INS-2, etc.). After that, I will try to go back and enter in information for the observational studies, like EOS, that don't already have records.

For FU, I am re-writing the description for this and adding in the new sites.

For Physiologic Definition, I believe this was originally under the Benchmarking study, which does have a record, but still needs to be updated. This will be "completed" for recruitment once the last eligible kid born before 5/1/2008 has been challenged (which should be in August when the last baby turns 36 weeks old). The Benchmarking record is NCT00067613. (FYI, you should be able to look up all of the NRN records by searching for "NICHD-NRN" under "Protocol ID.")

For Inositol, I've add Utah to the location list and Roger to the Study Investigators (the change will show up once it goes through the ClinicalTrials approval process). All sites with IRB approval should be listed as potential recruitment locations. FYI, we won't have a record for INS-2 until the protocol is finalized, which won't be until after we have results from INS-1.

Please let me know if you have any questions.

See you next week,

Stephanie

Stephanie Wilson Archer
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archerst@mail.nih.gov

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Monday, July 14, 2008 3:57 PM
To: Karen.Osborne@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]
Cc: Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

If any of the studies are listed then we should be added as a participating center.
Whether to add the others is questionable to me.

BAY

From: Karen Osborne RN
Sent: Monday, July 14, 2008 1:47 PM
To: 'Archer, Stephanie (NIH/NICHD) [E]'
Cc: Roger Faix; Bradley Yoder; higginsr@mail.nih.gov
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

As I'm going through the Clinical Trials.Gov site for the Network studies I have a few more questions.

The Follow-Up study (**Follow-Up Study of Extremely Low Birth Weight (ELBW) Infants**) does not list our site or any of the newer sites.

I realize that at this point Clinical Trials are only requiring interventional trials to be listed on their site. Is this why the BPD and EOS studies are not listed? Are there any plans to list them? Our University is encouraging us to list all studies which is why I'm asking.

And last of all, we are not listed under the Inositol study. We participated although did not enroll any patients. Should we be listed under this study?

Thanks for your help with this Stephanie!

Karen

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, July 14, 2008 7:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Karen Osborne RN; nfiner@ucsd.edu
Cc: Roger Faix; Bradley Yoder
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

Hi Karen,

Thanks for catching this. So many details in these records – and they keep changing the requested information on top of that!

I've made the changes and marked it as complete. I may be a week or two before it gets through the ClinicalTrials approval process.

Please let me know if I've missed anything on the other records, particularly the ongoing trials.

Thank you,

Stephanie

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 11, 2008 5:07 PM
To: 'Karen Osborne RN'; nfiner@ucsd.edu; Archer, Stephanie (NIH/NICHD) [E]
Cc: Roger Faix; Bradley Yoder
Subject: RE: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

We will add your site

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Friday, July 11, 2008 5:05 PM
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Roger Faix; Bradley Yoder
Subject: NCT00233324, NICHD-NRN-0031, Surfactant Positive Airway Pressure and Pulse Oximetry Trial

Hi Neil,

I have been dutifully going through the Network studies in Clinical Trials.gov to ensure that we are listed as appropriate and found that although Roger is listed as a Principle Investigator for the SUPPORT study, the U of Utah is not listed as a location. A simple oversight I'm sure, but one that I have to leave to you to remedy.

Thank you and have a good weekend!

Karen

Karen Osborne RN BSN CCRC
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT recruitment
Date: Friday, July 11, 2008 4:49:21 PM

Feel free to adjust

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Friday, July 11, 2008 4:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT recruitment

I checked the SUPPORT recruitment for the past 6 months against our projections. Several sites' recruitment numbers have fallen off since last year:

Indiana
Stanford
Duke
UCSD
Tufts

Those that have increased:

Dallas
Brown
Alabama
Houston
Utah

From: Auman, Jeanette O.
To: Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Budget | GDB for UCSD SUPPORT babies
Date: Tuesday, July 08, 2008 7:08:54 PM

Yup, I think I mentioned that I'd be adding Rochester's Inositol GDB numbers as well, which I have, but wanted to get this Hypo Extended follow-up completed visit vs. incomplete visit straight first.

I'd like to finish this up and get it off my desk! Thanks!

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, July 08, 2008 4:25 PM
To: Auman, Jeanette O.; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Budget | GDB for UCSD SUPPORT babies

No problem. I'll also need this for Rochester's Inositol babies.

I assume that both sites are aware of the Physiologic Definition being rolled into GDB now, right? I can't remember if Dale and Neil were included on Carolyn's emails about this.

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Tuesday, July 08, 2008 3:55 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: Budget | GDB for UCSD SUPPORT babies

Stephanie,

I think I already mentioned that I hadn't added them to the spreadsheet yet. I will send you the updated numbers as soon as we have the Hypo Extended follow-up specifications finalized.

Thanks!
Jenny

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, July 08, 2008 3:47 PM
To: Huitema, Carolyn Petrie; Auman, Jeanette O.; Zaterka-Baxter, Kristin
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Budget | GDB for UCSD SUPPORT babies

Hi Jenny,

I was looking through the numbers you already sent to me. UCSD doesn't have any GDB babies listed. Have they been turning in forms?

Stephanie

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, June 25, 2008 1:07 PM
To: 'Huitema, Carolyn Petrie'; Auman, Jeanette O.; Zaterka-Baxter, Kristin
Cc: Archer, Stephanie (NIH/NICHD) [E]

Subject: Budget | GDB for UCSD SUPPORT babies

I have this on the RTI-UCSD subcontract spreadsheet. I'm assuming all SUPPORT kids recruited by UCSD will need to complete GDB forms.

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Tuesday, June 24, 2008 4:20 PM
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: GDB

Just one comment.....since San Diego fell out of the network, they were funded additional money in the SUPPORT budget to collect "Baseline Data". It doesn't explicitly say GDB but that it was the money is for....SD to collect GDB data on SUPPORT infants.

From: Auman, Jeanette O.
Sent: Tuesday, June 24, 2008 2:27 PM
To: Zaterka-Baxter, Kristin; 'Archer, Stephanie (NIH/NICHD) [E]'; Huitema, Carolyn Petrie
Cc: Auman, Jeanette O.
Subject: RE: GDB

Hi Stephanie,

I'm attaching the numbers I have programmed so far. I still have to finish up getting the Follow-up numbers and Inositol Single dose (I've highlighted the rows I still need to do). Also, I had to add a row for "*First interview done by Rochester (through 2/29/2008)", since Rochester did some first interviews over the phone that the originating hospital could not do.

Regarding, GDB and which patients are counted as enrolled based on enrollment critiera, study enrollment, etc.

Prior to 1/1/2008 for **Support**, Centers were requested to complete the GDB for Support patients even if they were > 1500g. During data processing those >1500g patients were moved from the larger GDB dataset into a "Support Only" GDB data set, so they were NOT included in the main GDB count in the monthly report. On and after 1/1/2008, Support became an approved trial, so any patient eligible and randomized into Support is automatically eligible for GDB, so there is no need to separate the data.

San Diego is a unique Center, since they are enrolling new Support patients since becoming a "collaborating" Center. Their GDB data from the point they began re-enrolling and still are also parsed out of the larger GDB data set and not included in the monthly report GDB count. This is why I wanted to add a "Support Only GDB" line in the capitation spreadsheet, so these counts could be included there. Let me know what/where we should put those numbers.

For **EOS**, no GDB forms were completed if the patient did not meet the GDB weight requirement. This is still in effect even with the new criteria, so if there is no GDB data, they can not be counted in GDB. The centers are following this requirement. I double checked and NO EOS patients who do NOT meet GDB eligibility are keyed in the GDB data.

I think the Centers are following the eligibility requirements for all the protocols and are keying the data as they should, there are many edits to guide them and we put checks in the monthly report to count patients that really should be counted.

Let me know if you'd like to talk about the spreadsheet and what is in it/what is included/what's not included, etc. I am available tomorrow at 9:30 – 10:45 and 1 – 2:30.

Thanks!

Jenny

Jeanette Auman
Reasearch Programmer/Analyst
(919) 237-1213
joa@rti.org

From: Zaterka-Baxter, Kristin
Sent: Tuesday, June 24, 2008 1:21 PM
To: 'Archer, Stephanie (NIH/NICHD) [E]'; Huitema, Carolyn Petrie
Cc: Auman, Jeanette O.; Das, Abhik
Subject: RE: GDB

It is my understanding that there is no explicit cut off for trial babies, intentionally; just that they are of the premature population.

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, June 24, 2008 1:03 PM
To: Huitema, Carolyn Petrie
Cc: Auman, Jeanette O.; Zaterka-Baxter, Kristin
Subject: RE: GDB

In addition, have any forms for kids over 1500g been submitted? If so, for which trial(s)?

I am mainly concerned that everyone (PIs, Coordinators, etc.) be on the page about the inclusion of trial babies in GDB. If the cut off is 1500g for trial babies, then we need to be explicit about this.

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Tuesday, June 24, 2008 12:58 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Auman, Jeanette O.; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: GDB

Hi All-

I am including Jenny and Kris in this email so as to fully answer all Stephanie's questions.
Please let me know if I anything is incorrect.

For GDB, Rose asked that all GDB kids less than 1500g be funded. (old GDB criteria).

New Criteria
*Babies born on or after January 1, 2008 will be included in the GDB if they satisfy **any one** of the following:*
- *Inborn and between 22 0/7 to 28 6/7 weeks (<29 weeks) inclusive gestational age*
- *Inborn and between 401 grams to 1000 grams inclusive birth weight*
- *Enrolled in an NRN randomized trial or prospectively planned observational study.*

Therefore, for infants > 1000 grams who are in trials, GDB data will need to be collected. Infants weighing < 401 grams within the 22 0/7 to 28 6/7 weeks (<29 weeks) gestational age range are included.

I do not know how the GDB numbers in the monthly report are constructed
(ie, this probably includes the BW (401-100g) and GA (<29wks) criteria babies, but not sure about trial babies outside this range)

By Study:

not responsive - unrelated to SUPPORT

[redacted]

SUPPORT
Under the current GDB inclusion criteria, all SUPPORT patients should have GDB forms completed since they are less than 28wks GA.
However, under the old GDB inclusion criteria, some of the SUPPORT patients were over 1500g.
-If those kids over 1500g are not to be funded, are they to be included in the SUPPORT budget under Baseline Data?

not responsive - unrelated to SUPPORT

[redacted]

Carolyn Huitema

Research Analyst
RTI International
(301) 270-6664
petrie@rti.org

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT
Date: Wednesday, July 02, 2008 6:59:06 PM

(b) – We finally made contact with mother after several months of tracking and did a home visit last week. Data entered and was included in this week's transmission.
(b) – NG03 and NG07 entered
(b) – missed keying NG07 but was entered today.

Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 19, 2008 3:15 PM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.; Vivien Phillips
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed
CENTER	NETWORK	BPD_message
16	(b)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
16	(b)	Infant has been discharged and was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is not entered

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Das, Abhik; Gantz, Marie; Ellen Hale
Subject: FW: FW: Support SAE
Date: Wednesday, July 02, 2008 9:37:01 AM

Hi all,
Please see below for Dr. Avery's comments regarding the SAE at Emory; no further action is required at this point and RTI will continue to monitor these events.
Thanks,
Kris

From: Gordon Avery [mailto:gavery123@gmail.com]
Sent: Tuesday, July 01, 2008 2:27 PM
To: Zaterka-Baxter, Kristin
Subject: Re: FW: Support SAE

I have reviewed the report. The outcome, although unfortunate, was well within the clinical range for the underlying conditions being treated. As a single case, it does not indicate a trend requiring investigation or intervention. Gordon Avery

On Tue, Jul 1, 2008 at 12:08 PM, Zaterka-Baxter, Kristin <kzaterka@rti.org> wrote:

Hi Dr. Avery,

Dr. Higgins requested I send you this Support study Serious Adverse Event (SAE) attached as it was determined to be at least possibly related to study. We have asked the institution where the event occurred to notify their IRB as well. Please let me know if you feel further action is required at this point.

Thanks,

Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 01, 2008 11:38 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: RE: Support SAE

I agree - serious, but not unexpected. Did Ellen send it to their IRB? Also, Dr. Avery should review this to make sure we don't need to inform the other IRBs.

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]

Sent: Tue 7/1/2008 11:36 AM

To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: Das, Abhik; Gantz, Marie; nfiner@ucsd.edu

Subject: Support SAE

Hi,

Please find attached an SAE for the Support study from Emory that had attribution of possibly related to study. Though this is a serious event, I don't believe this is unexpected but wanted to make sure you all were aware of the event.

Thanks,

Kris

Kris Zaterka-Baxter

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www.rti.org <http://www.rti.org/>

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Kris Zaterka-Baxter

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3040 Cornwallis Road

RTP, NC 27709 USA

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Support SAE
Date: Tuesday, July 01, 2008 5:52:25 PM

I agree
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 01, 2008 8:38 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik; Gantz, Marie; Finer, Neil
Subject: RE: Support SAE

I agree - serious, but not unexpected. Did Ellen send it to their IRB?
Also, Dr. Avery should review this to make sure we don't need to inform the other IRBs.
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tue 7/1/2008 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: Support SAE

Hi,

Please find attached an SAE for the Support study from Emory that had attribution of possibly related to study. Though this is a serious event, I don't believe this is unexpected but wanted to make sure you all were aware of the event.

Thanks,

Kris

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

P.O. Box 12194

RTP, NC 27709-2194 USA

(tel) 919-485-7750

(fax) 919.485.7762

kzaterka@rti.org <mailto:kzaterka@rti.org>

www.rti.org <http://www.rti.org/>

Federal Express/UPS/DHL Shipping Address:

Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

RTP, NC 27709 USA

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie; nfiner@ucsd.edu
Subject: Support SAE
Date: Tuesday, July 01, 2008 11:36:09 AM
Attachments: Emory_SAE_01July2008.pdf
Importance: High

Hi,
Please find attached an SAE for the Support study from Emory that had attribution of possibly related to study. Though this is a serious event, I don't believe this is unexpected but wanted to make sure you all were aware of the event.
Thanks,
Kris

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3040 Cornwallis Road
RTP, NC 27709 USA

Neonatal Research Network
Emory University
P.O. Box 26015
[redacted]
Atlanta, GA 30303

facsimile transmittal

To: Kris Zaleska-Baxter Fax: 919-485-7762

From: Ellen Hale Date: 6/30/08

Re: Pages: 3

☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Comments:

SAE for SUPPORT.

Ellen Hale

Phone 404-616-4218 * FAX 404-524-3953

June 30, 2008

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

RE: Severe Adverse Event

Center 09 Rand. [redacted] Network (b) (6)

On 6/27/2008 antenatal signed informed consent and HIPPA authorization were obtained from this mother for this study in anticipation of delivery prior to 28 weeks gestation. This mother had rupture of membranes on (b) (6). Prior to delivery, she was treated with antibiotics and she received a full course of antenatal steroids (Betamethasone). Mother developed chorioamnionitis and an emergency Cesarean section was performed on (b) (6) 0319. This infant was randomized to the "Early Extubation and CPAP" arm of this NICHD study. This infant was a 900 gram female infant of 27 3/7 weeks gestation. She had APGAR scores of 8 at one minute and 9 at five minutes. She was placed on CPAP in the delivery room and taken to the NICU. She was placed on a Masimo study pulse oximeter (serial #323085). Septic work-up was performed on admission and antibiotics were initiated (blood cultures remain negative). During her first night, this infant remained on CPAP but began to have increased acidosis requiring normal saline boluses and her oxygen requirement reached 70-80%. She was having moderate retractions as well. Chest x-ray revealed a coarse reticular granular pattern throughout the lung fields with questionable PIE. The decision was made to intubate and place the infant on conventional ventilation and she was given a dose of surfactant. Following intubation, this infant had sudden decompensation and severe increased work of breathing. Chest x-ray revealed left side pneumothorax which resolved with needle aspiration. Later that day, this infant was placed on high frequency ventilation. On (b) (6) this infant remains on HFV. This case was reviewed with Dr. Anthony Piazza and cause of event could possibly be attributable to SUPPORT Study.

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
MEDWATCH FORM

SUPP08A Rel 1.0
January 4, 2005

Center: 09 (b) (6) Network No. (b) (6) Birth No: 1 Mother's Initials: ___ Page 1 of 1

SEND TO RTI AND NICHD WITHIN 24 HOURS

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier: (b) (6) In confidence
2. Age at time of event: or Date of birth: (b) (6)
3. Sex: ☒ female ☐ male
4. Weight: ___ lbs or 0.900 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ___ (mm/dd/yy)
   - ☒ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ___
3. Date of event (mm/dd/yy): 6/28/08
4. Date of this report (mm/dd/yy): 6/30/08
5. Describe event or problem

See attached report

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) (mm/dd/yy or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
   -
10. Concomitant medical products and therapy dates (exclude treatment of event)

N/A

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address

N/A

4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ___
5. Expiration date (mm/dd/yy)
6. model # ___ catalog # ___ serial # ___ lot # ___ other #
7. If implanted, give date (mm/dd/yy)
8. If explanted, give date (mm/dd/yy)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ___ (mm/dd/yy)
10. Concomitant medical products and therapy dates (exclude treatment of event)

Masimo Study Pulse Oximeter

E. Reporter (see confidentiality section on back)

1. Name & address
   Ellen Hale, RN
   P.O. Box 24015
   80 Jesse Hill, Jr. Dr.
   Atlanta, GA 30303
   phone # 404-616-4218
2. Health professional? ☒ yes ☐ no
3. Occupation: Research nurse Coord
4. Also reported to
   - ☐ manufacturer
   - ☒ user facility
   - ☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. ☒

FDA Form 3500

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

From: Finer, Neil
To: Brian Darlow; Schmidt, Barbara (Neonatology); Michelle.Gabriel@npeu.ox.ac.uk; laskie@ctc.usyd.edu.au; Ben.Stenson@luht.scot.nhs.uk; williamtm@med.usyd.edu.au; Peter.Brocklehurst@npeu.ox.ac.uk
Cc: robertsr@mcmaster.ca; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Masimo information
Date: Thursday, June 26, 2008 4:54:34 PM

I will be available at whatever works for the others
Neil

-----Original Message-----
From: Brian Darlow [mailto:brian.darlow@otago.ac.nz]
Sent: Thursday, June 26, 2008 1:07 PM
To: Schmidt, Barbara (Neonatology); Finer, Neil;
Michelle.Gabriel@npeu.ox.ac.uk; laskie@ctc.usyd.edu.au;
Ben.Stenson@luht.scot.nhs.uk; williamtm@med.usyd.edu.au;
Peter.Brocklehurst@npeu.ox.ac.uk
Cc: robertsr@mcmaster.ca; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Masimo information

Thank you Barbara - those dates would be suitable for me.
Kind regards, Brian

At 05:29 a.m. 27/06/2008, Schmidt, Barbara (Neonatology) wrote:
>Thanks, Neil!
>
>It looks as if the information will come our way very soon.
>
>I do believe that we cannot have a meaningful conference call without
>the information from Masimo, and without a few additional days of
>reflecting on it.
>
>Haste in this case would likely do more harm than good because any
>conclusions would be based on incomplete evidence.
>
>We also have to be able to put our trust in the SUPPORT DSMB. They
have
>been able to monitor a large number of babies to date and have not
>apparently had any concerns about safety.
>
>Could we reschedule the conference call please, for some time between
>July 8 and 15th? I believe that would also enable Brian Darlow to join
>who has told us that he would not be able to make it on June 30th.
>
>Barbara
>
>-----Original Message-----
>From: Michael OReilly [mailto:MOReilly@masimo.com]
>Sent: Thursday, June 26, 2008 1:01 PM
>To: Finer, Neil; Schmidt, Barbara (Neonatology);
>Michelle.Gabriel@npeu.ox.ac.uk; laskie@ctc.usyd.edu.au;
>Ben.Stenson@luht.scot.nhs.uk; williamtm@med.usyd.edu.au;
>Peter.Brocklehurst@npeu.ox.ac.uk; brian.darlow@otago.ac.nz
>Cc: robertsr@mcmaster.ca; Joe Kiani; Higgins, Rosemary (NIH/NICHD) [E];
>Mike Petterson; Ammar Al-Ali; Valerie Begnoche

>Subject: RE: Masimo information
>
>Dr. Finer and colleagues,
>
>We are meeting tomorrow to finalize our communication. You will be
>hearing from shortly thereafter.
>
>We appreciate your patience.
>
>Michael
>
>Michael O'Reilly, M.D. M.S.
>Executive Vice President for Medical Affairs
>Masimo Corporation
>
>Professor of Anesthesiology
>University of California at Irvine
>
>949-812(b) mobile
>
>
>-----Original Message-----
>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Thursday, June 26, 2008 9:09 AM
>To: Schmidt, Barbara (Neonatology); Michelle.Gabriel@npeu.ox.ac.uk;
>laskie@ctc.usyd.edu.au; Ben.Stenson@luht.scot.nhs.uk;
>williamtm@med.usyd.edu.au; Peter.Brocklehurst@npeu.ox.ac.uk;
>brian.darlow@otago.ac.nz; Michael OReilly
>Cc: robertsr@mcmaster.ca; Joe Kiani; Higgins, Rosemary (NIH/NICHD) [E]
>Subject: RE: Masimo information
>
>Hello Michael
>It has been a week since we spoke. All of the investigators, including
>the NICHD Research Network would like to see a clear explanation from
>Masimo regarding the dip in SpO2 values. We are all anxious to move
>ahead and would like whatever detail you can provide.
>Please let us know when we can expect to hear from Masimo.
>Regards
>Neil Finer
>
>Neil N. Finer, M.D.
>Professor of Pediatrics
>Director, Division of Neonatal-Perinatal Medicine UC San Diego School
of
>Medicine UC San Diego Medical Center, Hillcrest
>402 Dickinson St., MPF 1-140
>San Diego, CA 92103-8774
>Telephone: 619.543-3759
>Facsimile: 619.543.3812
>
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>
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>delete the original message.

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, June 26, 2008 12:39:54 PM

Yes, since the infant was in oxygen and not eligible for challenge.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 26, 2008 12:38 PM
To: Gantz, Marie
Subject: Fw: SUPPORT

Can this one be coded as Physio BPD?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Mackinnon, Brenda <BMackinnon@tufts-nemc.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Jun 26 12:07:21 2008
Subject: SUPPORT

Hi Rose,
This patient is still in house so this won't be entered for approx another month. This baby was in oxygen but didn't meet the criteria to be tested as the majority of the sats were too low the 24 hours prior to planned testing.

Thanks
Brenda

We are missing a few support outcomes. Thanks for all the effort!!!
Rose
CENTER NETWORK BPD_message
23 (b) (6) Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health

6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

We've performed a little surgery on our name.
Tufts-New England Medical Center is now Tufts Medical Center.
Please update your files with my new contact information. Thank you!

Brenda MacKinnon, RNC, NRN Coordinator
Floating Hospital for Children at Tufts Medical Center
800 Washington Street
Newborn Medicine, Floating 2, Box 44
Boston, MA 02111

Beeper (b)

Phone: 617-636-1218
Fax: 617-636-1456
bmackinnon@tuftsmedicalcenter.org

From: Walsh, Michele
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Das, Abhik; Auman, Jeanette O.; Huitema, Carolyn Petrie; nancy newman
Subject: RE: Another Support question
Date: Tuesday, June 24, 2008 3:34:57 PM

I think we will have to send out a technical memo to
Cover the situation of surgery, which is clearly not BPD.
For those not challenged because of instability, then we
Have to fall back on the baseline treatment at 36 weeks.
Michele

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 24, 2008 12:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele
Cc: Gantz, Marie; Das, Abhik; Auman, Jeanette O.; Huitema, Carolyn Petrie; nancy newman
Subject: RE: Another Support question

This can up as well and is related to the discussion below:

This also goes to the question of how we should classify infants who are not challenged because of instability (including surgery or sepsis). We don't have any SUPPORT infants coded that way yet on PHY01/new NG07, but it could happen (and there are non-SUPPORT babies with that code).

Thanks again,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 24, 2008 12:43 PM
To: Zaterka-Baxter, Kristin
Cc: Michelle Walsh
Subject: RE: Another Support question

I defer to Michele – if we record "on the vent" at 36 weeks, he is classified as BPD according to the old def of O2 at 36 weeks, but was on the vent for a procedure.
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 24, 2008 12:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Another Support question

HI,
Page 5-1 in the MOP says to record the highest type of support on the day of 36 weeks..... (please see below):

A) By SNAPSHOT- recording the respiratory support at exactly 24 hours and highest level of support **on day of 36 weeks postmenstrual age**. If the infant reaches Status (death, discharge, transfer) before any time point(s), no data is entered for the missed time point(s).

At 36 weeks postmenstrual age:
Questions #1-4- record 'Y' for the highest type of support the infant is receiving for

the day of 36 weeks postmenstrual age (i.e. if the infant was receiving conventional ventilation (CV) and high frequency ventilation (HFV) **on the day of 36 week** postmenstrual age, count only the HFV for that day). The hierarchy for support will be HFV as highest, CV as next, nasal SIMV next, then CPAP as lowest type of support.

Do you still want to wait a day or two; we've historically said they need to get this info on that one day (also on page .
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 24, 2008 12:30 PM
To: Zaterka-Baxter, Kristin; Mcdavid, Georgia E
Cc: Michele Walsh; nancy newman; Gantz, Marie
Subject: RE: Another Support question

Was he in oxygen the day following surgery? It is 36+1 week corrected age according to the manual – give him a day or two prior to coding him.

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 24, 2008 12:22 PM
To: Mcdavid, Georgia E
Cc: Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]; nancy newman; Gantz, Marie
Subject: FW: Another Support question

Hi Georgia,

The consensus here would be to code the baby as on the vent at 36 weeks reflecting the event in the relevant questions on the NG07, then F5 and comment. I've copied Michele, Rose and Nancy for their in put on a question Marie Gantz brought up about the definition of BPD and which to follow, the letter or the intention of the definition? By intention, we might not classify this infant as BPD, but by the letter of the definition he was on vent at 36 weeks.

Thanks and please send me the ID of this baby so we can make a note.

Kris

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Thursday, June 12, 2008 6:39 PM
To: Zaterka-Baxter, Kristin
Subject:

Here's another – we have a baby that was on RA for weeks prior to his 36 week day. On the day of the 36 weeks he went to surgery. Post op he remains on the ventilator > 4 hours. On the NG07 it needs to be coded as a vent day however for the Phys Def he would not have been on a vent if he did not go to surgery. I do not think he should be coded as BPD but he will because it is unlikely if we say yes to being on the vent for question B4 on the PHY01 we cannot comment other than to F5. Do those really get read when you are determining BPD %? I don't think so. Confusion abounds here in humid Houston. ☺

Georgia McDavid, R.N.

Senior Research Nurse-pediatrics/neonatology
Nurse Coordinator - NICHD Neonatal Network
MSB 3.252
office: 713-500-5734
office fax: 713-500-5794

Visit us at www.UHhospitals.org.

From: Mcdavid, Georgia E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Another Support question
Date: Tuesday, June 24, 2008 2:38:12 PM

That's how he will be coded but that would be inaccurate. He had been on RA for over a month prior to being intubated for surgery which just so happened to be on his 36 week date. If he had not gone to surgery on that day he would have been on RA at 36 weeks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 24, 2008 1:33 PM
To: Mcdavid, Georgia E
Subject: RE: Another Support question

Sounds like he had BPD by the standard definition

Rose

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Tuesday, June 24, 2008 2:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Another Support question

He ended up being on the vent for the entire week. He initially went to surgery for a reanastomosis on his 36 week date. 2 days later he ruptured and he had an ostomy and drain placed. Then because of pain meds he did not wean as his wound was open and they were gradually trying to close it. He went back to surgery one week later to try reanastomosis again. He is now 10 days later back on RA. It's been a tough 10 days for him.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 24, 2008 11:30 AM
To: Zaterka-Baxter, Kristin; Mcdavid, Georgia E
Cc: Michele Walsh; nancy newman; Gantz, Marie
Subject: RE: Another Support question

Was he in oxygen the day following surgery? It is 36+1 week
corrected age according to the manual – give him a day or two prior to coding him.

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 24, 2008 12:22 PM
To: Mcdavid, Georgia E
Cc: Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]; nancy newman; Gantz, Marie
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From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Thursday, June 12, 2008 6:39 PM
To: Zaterka-Baxter, Kristin
Subject:

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Georgia McDavid, R.N.
Senior Research Nurse-pediatrics/neonatology
Nurse Coordinator - NICHD Neonatal Network
MSB 3.252
office: 713-500-5734
office fax: 713-500-5794

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Mcdavid, Georgia E
Cc: nancy newman; Gantz, Marie
Subject: RE: Another Support question
Date: Tuesday, June 24, 2008 12:33:35 PM

I agree with Rose: see what happens and does he get back off.
It is an issue for the GDB: we should probably put the same exclusion in
For the child with the rare trip on the vent.
Michele

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 24, 2008 12:30 PM
To: Zaterka-Baxter, Kristin; Mcdavid, Georgia E
Cc: Walsh, Michele; nancy newman; Gantz, Marie
Subject: RE: Another Support question

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Sent: Tuesday, June 24, 2008 12:22 PM
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Cc: Michele Walsh; Higgins, Rosemary (NIH/NICHD) [E]; nancy newman; Gantz, Marie
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Kris

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Sent: Thursday, June 12, 2008 6:39 PM
To: Zaterka-Baxter, Kristin
Subject:

Here's another – we have a baby that was on RA for weeks prior to his 36 week day. On the day of the 36 weeks he went to surgery. Post op he remains on the ventilator > 4 hours. On the NG07 it needs to be coded as a vent day however for the Phys Def he would not have been on a vent if he did not go to surgery. I do not think he should be coded as BPD but he will because it is unlikely if we say yes to being on the vent for question B4 on the PHY01 we cannot comment other than to F5. Do those really get read when you are determining BPD %? I don't think so. Confusion abounds here in humid Houston. ☺

Georgia McDavid, R.N.
Senior Research Nurse-pediatrics/neonatology

Nurse Coordinator - NICHD Neonatal Network
MSB 3.252
office: 713-500-5734
office fax: 713-500-5794

Visit us at www.UHhospitals.org.

From: Cunningham, Meg
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; wrich@ucsd.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Martinez, Fernando; msumner@peds.uab.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio; Huitema, Carolyn Petrie
Subject: Reminder: Support Call
Date: Tuesday, June 24, 2008 8:21:43 AM

Reminder for today's call.

From: Cunningham, Meg
Sent: Friday, June 20, 2008 8:15 AM
To: 'nfiner@ucsd.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Gantz, Marie; 'wrich@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mcw3@cwru.edu'; 'Bradley Yoder'; 'Roger.Faix@hsc.utah.edu'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'nancy newman'
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; 'Martinez, Fernando'; 'msumner@peds.uab.edu'; 'sharon.gough@hsc.utah.edu'; 'Brenda Vecchio'; Huitema, Carolyn Petrie
Subject: Support Call

All-

The SUPPORT call will be on Tuesday, June 24th at 3:00pm ET, the Steering Committee call scheduled for Tuesday will follow right after this call at 3:30pm.

Dial:

Within the USA
866-675(b)
or
Outside the USA
1-203-310(b)

Then, enter Participant Passcode:
(b) (6)

Thanks,
Meg

From: Cunningham, Meg
Sent: Wednesday, June 18, 2008 5:14 PM
To: 'nfiner@ucsd.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Gantz, Marie; 'wrich@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mcw3@cwru.edu'; 'Bradley Yoder'; 'Roger.Faix@hsc.utah.edu'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'nancy newman'
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; 'Martinez, Fernando'; 'msumner@peds.uab.edu'; 'sharon.gough@hsc.utah.edu'; 'Brenda Vecchio'; Huitema, Carolyn Petrie
Subject: Urgent Support Call Needed
Importance: High

All-

We need an urgent SUPPORT conference call to discuss oximeter skew this coming Tuesday. ***Please send your availability for Tuesday, June 24th, indicating time zone if other than ET as soon as possible***. Rose will email around handouts prior to the call.

Thanks,
Meg

From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OUTCOMES
Date: Monday, June 23, 2008 10:31:30 AM

I wish, we had a really tough time and they were already out of window when we got them for the follow-up. We have tried to contact them several times and have not been able to find them again. I am not even sure we will have any luck getting them back for the 6-7 year follow-up.We will call and see what we get.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 06/23/08 8:05 AM >>>
Janet
Is there any way you could get them back for a Bayley III?
Thanks for taking the time to send this.

regards,
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

From: Janet Morgan [mailto:Janet.Morgan@UTSouthwestern.edu]
Sent: Mon 6/23/2008 8:53 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT OUTCOMES

Rose,
This is a set of twins that we have discussed before, they were mistakenly given the Bayley II instead of III, the form for Bayley II was completed on these twins and I will not have a NF09a. Sorry for that and please feel free to let me know if there is something else I need to do about this.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 06/19/08 3:02 PM >>>
We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER

NETWORK

FU_message

4

(b)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: URGENT and CONFIDENTIAL
Date: Monday, June 23, 2008 9:38:36 AM

In spite of the rhetoric, nothing yet.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 23, 2008 6:19 AM
To: Finer, Neil
Subject: RE: URGENT and CONFIDENTIAL

Neil
Did Massimo send us anything? it looks like not yet.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sun 6/22/2008 7:05 PM
To: Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Rich, Wade; wcarlo@peds.uab.edu; mcw3@cwru.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Martinez, Fernando; msumner@peds.uab.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio; Huitema, Carolyn Petrie; Rich, Wade
Subject: FW: URGENT and CONFIDENTIAL

Hello Again
This is probably all that we will need to know or actually have to discuss this issue.
Regards
Neil

-----Original Message-----
From: Peter Brocklehurst [mailto:Peter.Brocklehurst@npeu.ox.ac.uk]
Sent: Friday, June 20, 2008 9:09 AM
To: Brian Darlow (brian.darlow@chmeds.ac.nz); William Tarnow-Mordi; Finer, Neil; barbara.schmidt@uphs.upenn.edu
Cc: Ben Stenson; Michelle Gabriel
Subject: URGENT and CONFIDENTIAL

Dear Barbara, Brian and William

I have attached a number of documents to this email which highlight a potentially very important problem with all of our oxygen targeting trials. Rather than repeat all of this issues again, I would refer you

to the document written by Ben Stenson entitled 'Discussion paper2'.

We initially discussed this problem with Neil Finer, as he was aware of this issue and SUPPORT has recruited the largest number of babies so far - his response is attached (RE BOOST II UK.rtf), including some data provided by Masimo in relation to this (USCD_2_.pdf). We have also done some more work looking at babies recruited in the UK (based on the first 57 babies with complete data - SaturationAnalysis_19Jun08.pdf).

Once you have time to digest this information - and potentially been able to look at the degree of separation you have been able to achieve in your own trials, can I suggest we arrange an urgent teleconference to discuss these issues? As there are a few of us, I would like to suggest just 2 of us from each of the trials get together to discuss what we do about this information - this will (a) limit the number of people on the teleconference but (b) I am also keen that we limit the 'fall-out' from this until we have had an opportunity to talk to each other and agree what we are each going to do about it. I hope you agree this sounds a reasonable first step.

I am aware that we all have widely different time zones but if you could email Michelle Garbriel (this email is copied to her) she will sort out a data and time. Hopefully we can do this early next week.

Many thanks.

Best wishes

Peter

Peter Brocklehurst
Professor of Perinatal Epidemiology
Director
National Perinatal Epidemiology Unit
University of Oxford
Old Road Campus
Headington
Oxford
OX3 7LF
Tel: 01865 289719
Fax: 01865 289720

PLEASE NOTE:
NPEU Safety of Birth Conference - 2 October 2008
Further details and booking form at: www.npeu.ox.ac.uk/conference

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Friday, June 20, 2008 3:52:13 PM

Rose,
See comments below.
Ellen
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	FU message
9	(b) (6)	FU marked as complete (per NF10/SF10) but NE09a has not been entered Dev. visit will be 8/1/08
9		FU marked as complete (per NF10/SF10) but NE09a has not been entered Dev. visit will be 8/1/08
9		FU marked as complete (per NF10/SF10) but NF09a has not been entered Rorm entered today.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use: Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

hlgginst@mail.nih.gov

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Cunningham, Meg
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; wrich@ucsd.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Martinez, Fernando; msumner@peds.uab.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio; Huitema, Carolyn Petrie
Subject: Support Call
Date: Friday, June 20, 2008 8:14:32 AM

All-

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Dial:

Within the USA
866-675(b)
or
Outside the USA
1-203-310(b)

Then, enter (b) (6)
560152 #

Thanks,
Meg

From: Cunningham, Meg
Sent: Wednesday, June 18, 2008 5:14 PM
To: 'nfiner@ucsd.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Gantz, Marie; 'wrich@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mcw3@cwru.edu'; 'Bradley Yoder'; 'Roger.Faix@hsc.utah.edu'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'nancy newman'
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; 'Martinez, Fernando'; 'msumner@peds.uab.edu'; 'sharon.gough@hsc.utah.edu'; 'Brenda Vecchio'; Huitema, Carolyn Petrie
Subject: Urgent Support Call Needed
Importance: High

All-

We need an urgent SUPPORT conference call to discuss oximeter skew this coming Tuesday. ***Please send your availability for Tuesday, June 24th, indicating time zone if other than ET as soon as possible***. Rose will email around handouts prior to the call.

Thanks,
Meg

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, June 19, 2008 4:20:00 PM

Thank you for the reminder.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 19, 2008 3:15 PM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.; Vivien Phillips
Cc: Gantz, Marie; Das, Abhik
Subject: SUPPORT

We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed
CENTER	NETWORK	BPD_message
16	(b)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
16	(b)	Infant has been discharged and was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is not entered

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: Das, Abhik; Fuller, Martha
Subject: RE: SUPPORT
Date: Thursday, June 19, 2008 4:18:04 PM

This pt has never come back in—we will complete the Supp 10 and indicate loss at 50 weeks. thanks

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.278.7856 (fax)
317.312.(b) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 19, 2008 4:11 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Fuller, Martha
Subject: SUPPORT

We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
12	(b)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Thursday, June 19, 2008 4:03:47 PM

We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
5	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
5	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT OUTCOMES
Date: Thursday, June 19, 2008 3:56:16 PM

We are missing a few support outcomes. Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		55 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

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

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes
Date: Thursday, June 19, 2008 10:54:07 AM
Attachments: Infants with missing outcomes 06-18-08.xls

Rose,

Attached is the list of infants who are missing SUPPORT outcomes this month. As you and Abhik have discussed, the report for ROP has been changed so that only infants who have reached 55 weeks PMA are included (instead of 50 weeks). The centers will still receive the old 50 week reminders in the missing forms report that Jenny generates.

Marie

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

Missing_FU

CENTER	NETWORK	FU_message
4	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed
4		FU marked as complete (per NF10/SF10) but NF09a has not been completed
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed
13		FU marked as complete (per NF10/SF10) but NF09a has not been completed
14		FU window has closed but NF05 and NF09a have not been completed
14		FU window has closed but NF05 and NF09a have not been completed
16		FU window has closed but NF05 and NF09a have not been completed
18		FU window has closed but NF05 and NF09a have not been completed
19		FU marked as complete (per NF10/SF10) but NF09a has not been completed
19		FU marked as complete (per NF10/SF10) but NF09a has not been completed
19		FU window has closed but NF05 and NF09a have not been completed
19		FU window has closed but NF05 and NF09a have not been completed
19		FU window has closed but NF05 and NF09a have not been completed

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: nfiner@ucsd.edu
Subject: RE: Urgent Support Call Needed
Date: Thursday, June 19, 2008 8:38:45 AM

I should have thought of this earlier, but would it have made more sense to have this call after Masimo made their writeup (on an explanation of what happened) available?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 18, 2008 5:25 PM
To: Cunningham, Meg; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie; wrich@ucsd.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; fmartinez@ucsd.edu; msumner@peds.uab.edu; sharon.gough@hsc.utah.edu; BVecchio@WIHRI.org; Huitema, Carolyn Petrie
Subject: Re: Urgent Support Call Needed

All availability prior to and including tuesday is welcome.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Cunningham, Meg <mcunningham@rti.org>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>; Gantz, Marie <mgantz@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; alaptook@WIHRI.org <alaptook@WIHRI.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; nancy newman <nxs5@case.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Martinez, Fernando <fmartinez@ucsd.edu>; msumner@peds.uab.edu <msumner@peds.uab.edu>; sharon.gough@hsc.utah.edu <sharon.gough@hsc.utah.edu>; Brenda Vecchio <BVecchio@WIHRI.org>; Huitema, Carolyn Petrie <petrie@rti.org>
Sent: Wed Jun 18 17:13:37 2008
Subject: Urgent Support Call Needed

All-

We need an urgent SUPPORT conference call to discuss oximeter skew this coming Tuesday. Please send your availability for Tuesday, June 24th, indicating time zone if other than ET as soon as possible. Rose will email around handouts prior to the call.

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich; elaine
Subject: Re: SUPPORT
Date: Tuesday, June 17, 2008 1:10:12 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> HI,
> Below is a list of missing support outcomes. Let us know how you are doing.
> This is current as of the 5/20 data entry.
> Thanks for all the hard work!!
> Rose

CENTER	NETWORK	ROP_message
13	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
13	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

Hi Rose, we have been trying to reach the 2 babies who need the final ROP status. One of them is not from this area and was discharged home from the transfer hospital and we have had some limitied contact with her over the phone. The mom told us the baby was seen by an opthamologist and was told that he was "far-sighted". We mailed her a letter to hopefully get the exam results from the ophthamologist. The second baby was seen in our eye clinic recently but left before she was examined (with her eyes dilated). She is scheduled for a well child visit tomorrow with Elaine Romano and we will hopefully be able to schedule another eye exam. I will keep you posted. thanks,
Monica

From: Gordon Avery
To: Zaterka-Baxter, Kristin
Cc: RJB6J@hscmail.mcc.virginia.edu; Christine A. Gleason; Willinger, Marian (NIH/NICHD) [E]; Clemons, Traci (NIH/NICHD); mikeross@ucla.edu; kant@unc.edu; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; Blaisdell, Carol (NIH/NHLBI) [E]; meganhb@u.washington.edu; bprice@obgyn.humc.edu; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: Re: NICHD NRN Support Trial DSMC review at 75% status
Date: Friday, June 13, 2008 5:04:09 PM

Oct 14 works for me. I have penciled it in. Gordon Avery

On Fri, Jun 13, 2008 at 4:10 PM, Zaterka-Baxter, Kristin <kzaterka@rti.org> wrote:

> Dear all,
>
> In light of everyone's schedules being so booked up, I thought I'd ask for one date in hope you all may be available for a 2 hour meeting (any time during the day) on Tuesday October 14th to be held in the Washington DC area? Dr. Avery would very much like to have an actual meeting this go round in stead of a teleconference so please let me know if you would be available.
>
> If you are not available, would you mind terribly sending me your availability for the following dates:
>
> October
>
> Monday 10/06
>
> Tuesday 10/07
>
> Wednesday 10/08
>
> Thursday 10/09
>
> Friday 10/10
>
> Monday 10/13
>
> Monday 10/20
>
> Tuesday 10/21
>
> Wednesday 10/22
>
> Thursday 10/23
>
> Friday 10/24

Thanks very much,

Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, June 02, 2008 5:34 PM
To: 'gavery123@gmail.com'; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com'; 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk'; 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'
Subject: NICHD NRN Support Trial DSMC review at 75% status

Dear all,

According to the anticipated enrollment for the NICHD NRN Support trial, we estimate that the next planned interim analysis at 75% infant status (status being the first of the following events; discharge, transfer, in hospital at 120 day or death) should be ready for review by the DSMC sometime between **August 27 and Sept 5, 2008**. Please let me know your availability around this time; this will most likely be an in-person meeting of the committee members in the Washington DC area unless there are any other suggestions or objections.

Thanks,

Kris

Please find attached for reference the last DSMC meeting minutes at 50% infant status.

Kris Zaterka-Baxter

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Kris Zaterka-Baxter

RTI International

3040 Cornwallis Road

RTP, NC 27709 USA

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support missing outcomes report
Date: Friday, June 13, 2008 1:44:02 PM

Rose:

There seems to be some rumbling from the sites about these reminders, specifically for the missing ROP outcomes. The issue seems to be that, in the cases of BPD and Follow Up outcomes, we send reminders to centers only when the infants are past-due to have the outcomes reported. However, for ROP we are doing this when babies have reached the 50 weeks mark, while the rule is that a baby can only be declared lost at 55 weeks. There seems to be a perception that the reminders are a chastisement of sort, when, for ROP, the outcome is not really missing because a visit can happen up to 55 weeks. I guess whenever they get these reminders, at least some coordinators feel that they need to key something, while, for ROP there may legitimately be nothing to key because they are tracking the case and trying to schedule something before the 55 weeks cutoff. We were thinking that a compromise may be to bring the ROP reminders that Marie prepares for you in line with those for BPD and follow up, and send them out only for babies who have reached the 55 weeks mark. That way, if the centers know an outcome is missing they can answer the question about "final acute status lost to FU at 55 weeks" and not get reminders for those cases. They would still get the missing outcome at 50 weeks messages in the missing forms reports that Jenny creates in the DMS.

Let me know what you think.
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
Phone: 301-770-8214
Fax: 301-230-4646

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: FW: NICHD NRN Support Trial DSMC review at 75% status
Date: Tuesday, June 10, 2008 2:19:51 PM

Hi Rose,
Please see below re. the difficulty of getting the DSMC together for the next Support review and the eminent retirement of Dr. Avery. As it stands now, I think we're going to try, if at all possible, for a 2 hour meeting from 3 to 5pm) the Tuesday before the SCM in Oct at the Bolger; please let me know your thoughts.
Thanks,
Kris

-----Original Message-----
From: Gordon Avery [mailto:(b) (6)
Sent: Tuesday, June 10, 2008 2:00 PM
To: Zaterka-Baxter, Kristin
Subject: Re: FW: NICHD NRN Support Trial DSMC review at 75% status

Hi, Kristin. A face to face meeting in October seems best to me. I probably will be retiring from the DSMC, and would like the final meeting face to face rather than by telephone. Right now, October is fairly open, except for Mondays. Let me know, and I will try to accommodate. Best.

Gordon Avery

On 6/10/08, Zaterka-Baxter, Kristin <kzaterka@rti.org> wrote:
> Hi Dr. Avery,
>
>
>
> Of the 5 committee members who have responded with their availability
> thus far, there is no available date for all between 08/27 - 10/05. We
> have a couple of options:
>
> 1. We could push the face-to-face meeting back to mid-late October.
> We could still send out the interim analysis late Aug/earl Sept with
> ~70% of ROP outcomes and 80% of BPD outcomes or, we could run the
> analysis in Oct though we would likely have ~75% of ROP and 85% of BPD
> outcomes.
> 2. We could query availability for a teleconference though we did
> promise to have at least one face-to-face meeting per year and this
> Support study review will likely be the last scheduled review for any
> NRN study in 2008.
>
>
>
> Please let me know your thoughts.
>
> Thanks,
>
> Kris
>
>
>
>
>
>
> _____
>
> From: Zaterka-Baxter, Kristin
> Sent: Monday, June 02, 2008 5:34 PM
> To: (b) (6) ; 'RJB6J@hscmail.mcc.virginia.edu'; 'Christine
> A. Gleason'; 'Willinger, Marian (NIH/NICHD) [E]'; 'tclemons@emmes.com';
> 'mikeross@ucla.edu'; 'kant@unc.edu'; 'merran.thomson@ic.ac.uk';
> 'mcallen@jhmi.edu'; 'blaisdellcj@nhlbi.nih.gov'
> Cc: 'meganhb@u.washington.edu'; 'bprice@obgyn.humc.edu'
> Subject: NICHD NRN Support Trial DSMC review at 75% status
>
>
>

> Dear all,
>
>
>
> According to the anticipated enrollment for the NICHD NRN Support trial,
> we estimate that the next planned interim analysis at 75% infant status
> (status being the first of the following events; discharge, transfer, in
> hospital at 120 day or death) should be ready for review by the DSMC
> sometime between August 27 and Sept 5, 2008. Please let me know your
> availability around this time; this will most likely be an in-person
> meeting of the committee members in the Washington DC area unless there
> are any other suggestions or objections.
>
>
>
> Thanks,
>
> Kris
>
>
>
> Please find attached for reference the last DSMC meeting minutes at 50%
> infant status.
>
>
>
> Kris Zaterka-Baxter
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>

From: Gantz, Marie
To: Johnson, Karen; Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Subject: RE: SUPPORT
Date: Thursday, June 05, 2008 3:37:46 PM

Hi Karen,

The message regarding the NG07 referred to the 36 week snapshot which should be filled out on either the old or new version of the form. I apologize for any confusion.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
[illegible]

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Thursday, June 05, 2008 3:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT

I just looked at the last one again, and at the revised tech memo regarding the new NG07. This child was born before May 1, so according to the May 8, 2008 revised memo, we completed the PHY forms and not the new NG07.
Karen

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 05, 2008 2:04 PM
To: Johnson, Karen; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT

Thanks for being complete!
Rose

From: Johnson, Karen [mailto:karen-johnson@uiowa.edu]
Sent: Thursday, June 05, 2008 3:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward
Cc: Gantz, Marie
Subject: RE: SUPPORT

Rose,
Our answers are below.
Karen

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 1:14 PM
To: Bell, Edward; Johnson, Karen
Cc: Gantz, Marie
Subject: SUPPORT

HI,
Below is a list of missing support outcomes. Let us know how you are doing.
This is current as of the 5/20 data entry. Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
24	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age. this was a data entry error. we fixed
24	(b) (6)	SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age. should be N. are we not supposed to enter N if they are <18 months?

CENTER	NETWORK	BPD_message
24	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered) We don't enter the NG07 until status. It will be entered then.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT randomization cards
Date: Thursday, June 05, 2008 10:46:17 AM

I think this case is similar to the one at Dallas; please see the email string below; there were several discussions and answers.
Thanks,
Kris

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 03, 2008 7:58 PM
To: Bradley Yoder; Karen Osborne RN; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT randomization cards

If this is categorized as a fetal death, then there is no issue and the infant would not be considered at a study patient
Neil

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Thursday, January 03, 2008 4:10 PM
To: Karen Osborne RN; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kzaterka@rti.org
Subject: RE: SUPPORT randomization cards

Sorry that I am late in the communication line on this case.
Although the randomization card was pulled in anticipation of an imminent birth....this was a fetal death....and is so being labeled by the attending MFM doc.
If we are not collecting information on fetal deaths as part of the Network GDB, we ought not to collect data on this patient either.

Brad

Brad Yoder
Dept of Peds/Neonatology
University of Utah
Phone 801-581-7052
Fax: 801-585-7395
Pager: 801-339(b) (6)
Email: bradley.yoder@hsc.utah.edu

From: Karen Osborne RN
Sent: Thursday, January 03, 2008 5:15 PM
To: Bradley Yoder
Subject: FW: SUPPORT randomization cards

Read from the first email I sent to Kris.
Thanks!

Karen

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 3:08 PM
To: Karen Osborne RN
Cc: Das, Abhik; Gantz, Marie
Subject: FW: SUPPORT randomization cards

Hi Karen,
The consensus below is that this infant should be enrolled in Support and both the Support and GDB forms completed; please complete the Supp03 as stated below (code 2 patient died under question 9).

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 03, 2008 4:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Rich, Wade; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT randomization cards

I agree
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 03, 2008 1:05 PM
To: Zaterka-Baxter, Kristin; Finer, Neil; Rich, Wade; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT randomization cards

It sounds like the child met all inclusion criteria and one of the exclusion criteria. I would say that the baby is included, but mark #2 patient died under question 9 on the SUPP03 form.

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 3:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wade Rich; Das, Abhik; Gantz, Marie
Subject: FW: SUPPORT randomization cards

Hi,
Please see below for details of the Support case mentioned earlier at Utah.
Thanks,
Kris

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Thursday, January 03, 2008 3:17 PM
To: Zaterka-Baxter, Kristin

Subject: RE: SUPPORT randomization cards

Actually what happened was (b) (6) [redacted] So no apgars were assigned as it was essentially a still birth even (b) (6) [redacted].

Does that help?

Karen

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 12:00 PM
To: Karen Osborne RN
Subject: RE: SUPPORT randomization cards

Hi Karen,
We need a bit more info; did the child have apgars assigned and was there resuscitation attempted?? Unless the baby was a stillbirth, he/she should be considered "enrolled." Please send as much detail as possible.
Thanks much,
Kris

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Thursday, January 03, 2008 11:37 AM
To: Zaterka-Baxter, Kristin
Subject: SUPPORT randomization cards

Hi Kris,

Happy New Year to you!

We had a baby that was delivering (b) (6) [redacted] who was signed up for the SUPPORT study, but unfortunately died during delivery. The randomization card had been pulled. What is the protocol for pulled, but not used randomization cards? I can't seem to find it in the MOP although I'm sure it's in there somewhere!

Thanks!
Karen

Karen Osborne RN BSN CCRC
Project Manager
Neonatal Research Network
University of Utah
Dept of Pediatrics, Division of Neonatology
PO Box 581289
Salt Lake City, UT 84158
Phone # (801)213-3298
Pager # (801) (b) (6) [redacted]
Fax # (801) 587-3618

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: SUPPORT Randomization #
Date: Thursday, June 05, 2008 10:03:14 AM

Hi Rose,
I spoke with Marie and Abhik about this case below and it sounds like the initial decision not to resuscitate was made prior to delivery so it would be correct to key "N" on A2 and then "0" on C1 on the Supp02 (basically calling the infant ineligible); then tuck that randomization card away for safe keeping. Does this sound correct to you as well and/or should I get further in put from Neil?
Thanks,
Kris

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Wednesday, June 04, 2008 5:33 PM
To: Zaterka-Baxter, Kristin
Subject: Re: FW: SUPPORT Randomization #

Kris,
I spoke to the Fellow and it sounds like it was a real mess.
The card was pulled with the intent to resuscitate. The Resus team was called back to delivery, pulled the card and while they were waiting the cord prolapsed. OB decided not to do a C/S and then they lost the HR It was decided that they would just let the baby go and the Resus. team left. Mom then got pitocin and the baby was born alive later but the decision was made not to resuscitate that time.
I was going to key it as a "N" on A2 and then "0" on C1. Do you agree? Or should I answer C1 as "1" and then add that the baby was not randomized due to prolapsed cord at delivery.
Thanks,
Nancy

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 6/4/2008 9:46 AM >>>
Hi Nancy,

Was there the intent to resuscitate when the card was pulled?

Thanks,

Kris

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]

Sent: Tuesday, June 03, 2008 2:29 PM
To: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Randomization #

Kris,

We have a randomization card that was pulled and then the baby wasn't resuscitated.

The randomization no. is #(b) (6)

Thanks,

Nancy

Nancy A. Miller, R.N.

Clinical Research Coordinator

Department of Pediatrics

Division of Neonatal-Perinatal Medicine

UT Southwestern Medical Center at Dallas

5323 Harry Hines Blvd. E3-404B

Dallas, Texas 75390-9063

214-648-3780

pager 972-206(b) (6)

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Tuesday, June 03, 2008 2:33:05 PM

(b) (6) moved out of state and hadn't had any eye exam and (b) (6) has not rescheduled missed follow up eye appt – final acute status coded as lost to follow up.
(b) (6) is due to come for the 18 month visit on Thursday, 6/5.
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 1:05 PM
To: wacarlo@uab.edu; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.; Vivien Phillips
Cc: Gantz, Marie
Subject: SUPPORT

HI,
Below is a list of missing support outcomes. Let us know how you are doing.
This is current as of the 5/20 data entry. Thanks for the continued outstanding recruitment!! This is amazing given the number of study subjects you have at the UAB site!!!
Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Reminder: SUPPORT Conference Call
Date: Tuesday, June 03, 2008 1:48:17 PM

Thanks: perhaps at the end we could talk about the BPCA issues.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 03, 2008 1:47 PM
To: Walsh, Michele
Subject: RE: Reminder: SUPPORT Conference Call

4 PM ET
866-675-(b) (6) with passcode (b) (6)

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, June 03, 2008 1:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Reminder: SUPPORT Conference Call

What time Rose? mw

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 03, 2008 12:29 PM
To: Cunningham, Meg; Webb, Robin E.; Das, Abhik; kurt.schibler@cchmc.org; alaptook@WIHRI.org; mcw3@cwru.edu; wcarlo@peds.uab.edu; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu; Zaterka-Baxter, Kristin; Poole, W. Kenneth; fmartinez007@mac.com
Cc: msumner@peds.uab.edu; fmartinez@ucsd.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: Reminder: SUPPORT Conference Call

For today's SUPPORT call

1. Protocol violations – see email trail below and the attached SUPP06. The DSMC has tracked the items on SUPP06.
2. Update from Meta-analysis meeting

Here is some information for today's call:
From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, May 15, 2008 2:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Poole, W. Kenneth
Subject: RE: Presentation from PAS

Rose:

The DSMC has seen these events by group (though blinded in the form of "ventilation arm groups A and B"), and did not express any specific concern related to this. In general, the total number of these types

of events ranged from 2-9 (some could be from the same baby) at the last look; so we are not talking about lots of violations here.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 15, 2008 1:24 PM
To: Das, Abhik; Gantz, Marie
Cc: Poole, W. Kenneth
Subject: RE: Presentation from PAS

If the DSMC sees these by group, I think we are fine. Also, are there site issues with these violations (i.e. more at one site or in specific arms than others)? And YES the DSMC would need to ok this.

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, May 15, 2008 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: nfiner@ucsd.edu; Poole, W. Kenneth
Subject: RE: Presentation from PAS

Rose:

These numbers are already periodically reported in the protocol deviation updates Marie creates for the subcommittee meetings. However, they are not presented by treatment group, like other study data. If we want the investigators to see this by treatment group, do we need to get an okay from the DSMC first?

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 15, 2008 12:27 PM
To: Das, Abhik; Gantz, Marie
Subject: FW: Presentation from PAS

Marie and Neil –
This may be able to be sorted out from the protocol deviation form by looking at the following questions between the CPAP and intubation/surfactant group. This will get at protocol compliance with respect to the ventilation arm of the protocol.

4. Mechanical ventilation initiated for other than study criteria.
5. NSIMV initiated in infant not previously intubated.
6. Extubation (exclude unplanned extubation) for other than study criteria?
7. Failure to extubate CPAP infant if all criteria met.

One further way to discern this would be to audit the safety monitoring forms to see if children were treated according to the protocol with respect to the CPAP and intubation arms.

Let me know what you think.

Rose

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, May 14, 2008 8:27 PM
To: Wally Carlo, M.D.; Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Ed Donovan; adas@rti.org
Subject: RE: Presentation from PAS

I would be happy to discuss this. I am not sure that this is an issue within SUPPORT but rather an issue potentially of willingness to enroll within the trial. None of the data presented is for SUPPORT infants if I read this correctly.
Before SUPPORT the individual NRN centers had very large variations in the practice of using early CPAP vs Surfactant, some of it published – ie Cincinnatti. The fact that this center has moved more to CPAP outside the trial cannot be interpreted as affecting the infants within the trial. It may affect the level of equipoise from this center. It is also of interest that they obviously have a very large number of what appear to be eligible infants not enrolled. Perhaps that is the more important issue
I will put this on the Agenda for our next meeting.
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, May 14, 2008 7:46 AM
To: Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Finer, Neil; Ed Donovan; adas@rti.org
Subject: RE: Presentation from PAS

Michele:

Thanks for bringing this up. I agree. This is important to address.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Wednesday, May 14, 2008 9:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Wally Carlo, M.D.; Neil_Finer" <; Ed Donovan; adas@rti.org
Subject: RE: Presentation from PAS

I saw the poster at PAS. I think this is a **big issue in support** that should be discussed on our next conference call. This work at UTSW shows evidence that the intervention (cpap) has spread to their non SUPPORT population, and thus draws in to question whether the control arm has been contaminated

at this site and other sites. Wally has raised this issue frequently since study inception. While we very carefully
track compliance on the oxygen saturation arm, we have done no assessment of protocol compliance in the cpap/ intubation arm. Could we plan a discussion?

Michele Walsh
phone: 216-844-3759

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 14, 2008 10:04 AM
To: bsood@med.wayne.edu; nfiner@ucsd.edu; Rich, Wade; Susie Buchter; Vivek.Narendran@cchmc.org; Vineet Bhandari; Susan Hintz; Brenda.H.Morris@uth.tmc.edu; Laroia, Nirupama; Phelps, Dale; Duara, Shahnaz; moshea@wfubmc.edu; Stevens, Timothy; Navarrete, Cristina; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa
Cc: Zaterka-Baxter, Kristin; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Huitema, Carolyn Petrie; Newman, Jamie
Subject: Presentation from PAS

Hi to all involved in SUPPORT,
I was asked by Pablo to send out the presentation from PAS from UT Southwestern.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, June 03, 2008 9:43 AM
To: Webb, Robin E.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@WIHRI.org; mcw3@cwru.edu; wcarlo@peds.uab.edu; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu; Zaterka-Baxter, Kristin; Poole, W. Kenneth
Cc: msumner@peds.uab.edu; fmartinez@ucsd.edu; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie
Subject: Reminder: SUPPORT Conference Call

Reminder for today's call.

From: Webb, Robin E.
Sent: Wednesday, May 28, 2008 9:33 AM
To: Webb, Robin E.; 'higginsr@mail.nih.gov'; Das, Abhik; 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; 'mcw3@cwru.edu'; 'wcarlo@peds.uab.edu'; 'Roger.Faix@hsc.utah.edu'; 'nfiner@ucsd.edu'; 'Bradley.Yoder@hsc.utah.edu'; Gantz, Marie; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'; Zaterka-Baxter, Kristin
Cc: 'msumner@peds.uab.edu'; 'fmartinez@ucsd.edu'; Cunningham, Meg; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: RE: SUPPORT Conference Call

The SUPPORT conference call has been scheduled for:

Tuesday, 6/3
4:00pm ET

Dial:

Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)

Then, enter Participant Passcode:
(b) (6)

Visit us at www.UHhospitals.org.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Subject: FW: Antenatal
Date: Tuesday, June 03, 2008 12:55:09 PM
Attachments: Apgars for SUPPORT vs GDB.rtf

Hi Everyone
I thought that this analysis would be of interest. We can briefly discuss on the call.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

Attached are cross-tabulations and chi-squared tests of the independence of Apgar score <4 (at 1 and 5 minutes) and enrollment in SUPPORT. Infants included are those that were 24-27 weeks GA and inborn 2005 to present. Note that for GDB infants not enrolled in SUPPORT, whether the infant had known congenital malformations prior to delivery and intention to resuscitate are not known.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Sunday, June 01, 2008 8:36 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: RE: Antenatal

Compare Apgar scores for SUPPORT infants vs. GDB infants inborn at 24-27 weeks 2005-present

The FREQ Procedure

Table of apgar1lt4 by support

apgar1lt4(1 minute Apgar <4)	support(Infant enrolled in SUPPORT)		
Frequency Col Pct	1=Yes	2=No	Total
1=Yes	359 34.55	1338 42.97	1697
2=No	680 65.45	1776 57.03	2456
Total	1039	3114	4153

Frequency Missing = 15

Statistic	DF	Value	Prob
Chi-Square	1	22.8282	<.0001

Table of apgar5lt4 by support

apgar5lt4(5 minute Apgar <4)	support(Infant enrolled in SUPPORT)		
Frequency Col Pct	1=Yes	2=No	Total
1=Yes	87 8.37	395 12.67	482
2=No	953 91.63	2722 87.33	3675
Total	1040	3117	4157

Frequency Missing = 11

Statistic	DF	Value	Prob
Chi-Square	1	14.1126	0.0002

Note: For GDB infants, whether the infant had known congenital malformations prior to delivery and intention to resuscitate are unknown

From: Fernando Martinez
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: fmartinez@ucsd.edu
Subject: Re: FW: Reminder: SUPPORT Conference Call
Date: Tuesday, June 03, 2008 11:09:09 AM

Thanks Dr. Higgins.

Fernando

On Tuesday, June 03, 2008, at 07:50AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>
>
>
>
>_____
>
>From: Cunningham, Meg [mailto:mcunningham@rti.org]
>Sent: Tuesday, June 03, 2008 9:43 AM
>To: Webb, Robin E.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik;
>kurt.schibler@cchmc.org; alaptook@WIHRI.org; mcw3@cwru.edu;
>wcarlo@peds.uab.edu; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu;
>Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu;
>Zaterka-Baxter, Kristin; Poole, W. Kenneth
>Cc: msumner@peds.uab.edu; fmartinez@ucsd.edu; Archer, Stephanie
>(NIH/NICHD) [E]; Huitema, Carolyn Petrie
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>To: Webb, Robin E.; 'higginsr@mail.nih.gov'; Das, Abhik;
>'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; 'mcw3@cwru.edu';
>'wcarlo@peds.uab.edu'; 'Roger.Faix@hsc.utah.edu'; 'nfiner@ucsd.edu';
>'Bradley.Yoder@hsc.utah.edu'; Gantz, Marie; 'nxs5@cwru.edu';
>'wrich@ucsd.edu'; Zaterka-Baxter, Kristin
>Cc: 'msumner@peds.uab.edu'; 'fmartinez@ucsd.edu'; Cunningham, Meg;
>'Archer, Stephanie (NIH/NICHD) [E]'
>Subject: RE: SUPPORT Conference Call
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>Then, enter Participant Passcode:
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>otherwise permitted by law.
>

From: Billian, Elizabeth
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Sood, Beena; Bara, Rebecca
Subject: SUPPORT
Date: Monday, June 02, 2008 7:57:21 PM

Babies with missing ROP exams:

(b) (6) and (b) (6) - I have spoken to the mother several times. She states she will schedule the eye exams but has not done so.

(b) (6) -this baby was transferred to another acute care facility; I spoke with the charge nurse who states no eye exams have been done thus far.

Betty Billian

From: Jensen, Rosemary
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale; Laroia, Nirupama
Cc: Gantz, Marie; Reubens, Linda; Burnell, Erica
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 7:13:07 PM

Hi Dr. Higgins,

Unfortunately this family has refused the follow-up assessment, but we are working on gathering some data for the NF12 from chart review.

Thank you for your patience,

Rosie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 5/29/2008 2:12 PM
To: Phelps, Dale; Laroia, Nirupama; Jensen, Rosemary
Cc: Gantz, Marie
Subject: SUPPORT

CENTER	NETWORK	FU_message
21	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

HI,
Above is a list of missing support outcomes. Let us know how you are doing.
This is current as of the 5/20 data entry.
Thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Auman, Jeanette O.
To: Bethany Ball; Higgins, Rosemary (NIH/NICHD) [E]
Cc: vanmeurs@leland.stanford.edu; Gantz, Marie; mproud@stanford.edu
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 2:40:23 PM

Hi Beth,

What was the date of the last exam which shows the mature retina diagnosis? The last exam date currently in our processed data is dated 2/19/2008.

Thanks,
Jenny

From: Bethany Ball [mailto:mbball@stanford.edu]
Sent: Thursday, May 29, 2008 2:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: vanmeurs@leland.stanford.edu; Gantz, Marie; Auman, Jeanette O.; mproud@stanford.edu
Subject: Re: SUPPORT

(b) (6) is expected to have an eye exam this summer. We continue to monitor her on an out-patient basis.

(b) (6) has mature retinas. These data were keyed and the form marked complete on 5/16/08. According to our records, there was a successful transmission on 5/20/08 at which time the data should have been received by RTI.

MBB

CENTER

NETWORK

ROP_message

15

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

15

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,

Above is a list of missing support outcomes. Let us know how you are doing.

This is current as of the 5/20 data entry.

Thanks for all the hard work!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

--

Bethany Ball
Division of Neonatal and Developmental Medicine
650.725.8342

From: Gantz, Marie
To: Ellen.Hale@oz.ped.emory.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 2:30:10 PM

Hi Ellen,

Thanks for the update on the infants with missing NF09a. For infant (b) (6), we have one exam with lowest zone of any vessels =3 in both eyes, but we need two consecutive exams with lowest zone =3 for status. The last exam entered was from 7/19/07. Is there another exam that has not been entered yet?

Thanks,

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

[redacted]

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 2:17 PM
To: Gantz, Marie; Auman, Jeanette O.
Subject: FW: SUPPORT

Do we have all of this?
Thanks
Rose

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Thursday, May 29, 2008 2:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

Rose,
See our comments below. Also, could you send Kris' home address?
Thanks,
Ellen

CENTER	NETWORK	ROP message
9	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Entered--eyes mature.

CENTER	NETWORK	EU message
9	(b) (6)	EU marked as complete (per NE10/SE10) but NF09a has not been completed Visit complete all but Bayley--scheduled in August.
9		EU marked as complete (per NE10/SE10) but NF09a has not been completed Visit complete all but Bayley--scheduled in August.
9		EU marked as complete (per NE10/SE10) but NF09a has not been completed Awaiting NF09 from examiner.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

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higginsr@mail.nih.gov

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 2:24:56 PM

Not as of the last data transmission (Tuesday 5/27), but I'll check next week. Also, looks like we'll probably only get the 1 possibly 2, the others are scheduled later.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 2:17 PM
To: Gantz, Marie; Auman, Jeanette O.
Subject: FW: SUPPORT

Do we have all of this?
Thanks
Rose

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Thursday, May 29, 2008 2:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

Rose,
See our comments below. Also, could you send Kris' home address?
Thanks,
Ellen

CENTER	NETWORK	ROP_message	
9	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye	
		Entered--eyes mature.	

CENTER	NETWORK	FU_message	
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed	
		Visit complete all but Bayley--scheduled in August.	
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed	
		Visit complete all but Bayley--scheduled in August.	
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed	
		Awaiting NF09 from examiner.	

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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[redacted]

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Cunningham, Meg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 2:20:19 PM

The only person who responded thus far is Georgia and she does not have blues. I will respond to them asking for oranges now. If I don't here anything in the next 30 minutes I will start calling.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 2:19 PM
To: Rich, Wade
Cc: Cunningham, Meg
Subject: RE: SUPPORT

Kris is out and I am checking with Meg.
We will find you some.

Rose

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Thursday, May 29, 2008 2:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Can we get 3 orange for Sharp ? They have trips.
wade

-----Original Message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "nfiner@ucsd.edu" <nfiner@ucsd.edu>; "Rich, Wade" <wrich@ucsd.edu>
Cc: "Gantz, Marie" <mgantz@rti.org>
Sent: 5/29/2008 11:11 AM
Subject: SUPPORT

CENTER

NETWORK

ROP_message

22

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

BPD_message

22

(b) (6)

Infant has been discharged and was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is not entered

HI,

Above is a list of missing support outcomes. Let us know how you are doing.

This is current as of the 5/20 data entry.

Thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.; Vivien Phillips
Cc: Gantz, Marie
Subject: RE: SUPPORT
Date: Thursday, May 29, 2008 2:09:35 PM

Rose:

Thanks for your encouragement and recognition of our nurses work.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 29, 2008 1:05 PM
To: wacarlo@uab.edu; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.; Vivien Phillips
Cc: Gantz, Marie
Subject: SUPPORT

HI,
Below is a list of missing support outcomes. Let us know how you are doing.
This is current as of the 5/20 data entry. Thanks for the continued outstanding recruitment!! This is amazing given the number of study subjects you have at the UAB site!!!
Thanks for all the hard work!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Thursday, May 29, 2008 2:03:06 PM

CENTER	NETWORK	ROP_message
15	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
15	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,
Above is a list of missing support outcomes. Let us know how you are doing.
This is current as of the 5/20 data entry.
Thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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301-496-5575
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higginsr@mail.nih.gov

From: Das, Abhik
To: Webb, Robin E.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Conference Call
Date: Wednesday, May 28, 2008 9:38:59 AM

I cannot make this one as well. Marie will attend, and I will see if Ken can fill in for me.

Thanks

Abhik

From: Webb, Robin E.
Sent: Wednesday, May 28, 2008 9:33 AM
To: Webb, Robin E.; 'higginsr@mail.nih.gov'; Das, Abhik; 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; 'mcw3@cwru.edu'; 'wcarlo@peds.uab.edu'; 'Roger.Faix@hsc.utah.edu'; 'nfiner@ucsd.edu'; 'Bradley.Yoder@hsc.utah.edu'; Gantz, Marie; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'; Zaterka-Baxter, Kristin
Cc: 'msumner@peds.uab.edu'; 'fmartinez@ucsd.edu'; Cunningham, Meg; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: RE: SUPPORT Conference Call

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Then, enter Participant Passcode:
(b) (6)

Visit us at www.UHhospitals.org.

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: That prospective NeOProM collaboration
Date: Wednesday, May 28, 2008 12:38:39 AM

Hi Rose
I agree with you and would support this approach
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 27, 2008 9:15 AM
To: Finer, Neil
Subject: FW: That prospective NeOProM collaboration

Neil
The sites that purchased the oximeters were to get them for their own use following re-configuration by Masimo. That being said, individual sites could agree to decide what to do with their individually purchased equipment. We can discuss on the SUPPORT Subcommittee call and present this to the steering committee. It may be in our interest to have the trial(s) proceed faster for the sake of the prospective meta-analysis.

Rose

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, May 26, 2008 10:24 AM
To: Edmund Hey; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade
Subject: RE: That prospective NeOProM collaboration

Hi Edmund
I agree with you that you need to start planning for this possibility. The intent for the Neonatal Research Network was that the converted monitors would remain the property of the individual units and that they would be converted back to regular oximeters. As a result this may provide a possibility that these could be leased/loaned etc to your trial before the conversion. I am still targeting about 9 months to completion which would mean that any oximeters unused at trial closure and subsequently the oximeters used on infants will become available as the infants come out of oxygen.
I will ask Rose if she sees any issues with this approach. I suspect that the decisions may need to be made by individual units, but I would like to begin to ask this question now.
Continued good luck with the trial
Be well
Neil

From: Edmund Hey [mailto:shey@easynet.co.uk]
Sent: Monday, May 26, 2008 7:04 AM
To: Finer, Neil
Cc: Rich, Wade
Subject: That prospective NeOProM collaboration

Neil,
I gather, from those who were there, that the meeting that Lisa Askie convened in Hawaii went well. It is

good to see all the trials recruiting well now. Even the UK is beginning to get moving at last after 18 months of largely mindless regulatory delay. Things have improved a lot in the last four weeks. The challenge for the UK trial is now going to be to recruit to target in a significantly shorter time frame than was originally intended, and the problem is going to be that, although Petwr Brocklehurst could probably find some more centres prepared to join the study, he is going to be limited as to how many babies he can have under active monitoring in the trial at any one time by the number of monitors he possesses. There had been a suggestion that the NPEU might go back to the MRC for supplementary finding in order to aquire a few more monitors but Masimo now tell us that they would not be able to support the conversion of any more monitors for trial use even if we had the money to be able to request this. That did just leave me wondering what was going to happen to the monitors you are using in SUPPORT once your study closes to recruimtent in about ten months time. Is there any hope at all that at least a coupe of dozen of these monitors could be leased or lent to the UK trial or even bought outright at a realistic 'second hand' price from your people ? It might make all the difference to Peter's team being able to recruit to target before their money runs out and/or the other parallel trials close to recruitment. I know it is looking ahead a bit, but somebody *needs* to do this ! If you could explore whether some option along these lines would be possible I really would be grateful.

Edmund

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: Missing SUPPORT outcomes
Date: Wednesday, May 21, 2008 2:44:32 PM
Attachments: Infants with missing outcomes 05-21-08.xls

Rose,

Attached is the list of infants who are missing SUPPORT outcomes this month.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
15		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
15		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
19		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Missing_ROP

19	(b) (6)	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.
22		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.
24		SUPP10 Q:'Final ROP status determined at 18M FU'=N but infant is <18 months adjusted age.

From: Gantz, Marie
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Antenatal Consent
Date: Monday, May 19, 2008 5:30:40 PM

Thanks, Neil and Wade, for looking at this. Your conclusion that the events are genuine agrees with Masimo's assessment that the oximeters in question were functional so I think we can assume that the units are OK.

Marie

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

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, May 19, 2008 5:15 PM
To: Gantz, Marie; Rich, Wade
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Antenatal Consent

Hi Marie
Wade and I have reviewed these tracings. To us, these events look real, that is the fall in Heart rate and the fall in pulse oximeter are aligned as one would expect for a real event. Artefactual changes happen much less with Heart rate than the oximeter tracing, and HR artefacts tend to be brief. Most oximeter false events are not associated with HR artefacts in our experience. We have seen such events in a recent study that we are completing suggesting that these infants are having events associated with both bradycardia and desaturation. Such events are frequent, even for infants on ventilators.
I understand that the unit is concerned that the events are not real, especially the deep desaturations, but I see little to suggest that these desaturations and associated bradycardias are not genuine.
We certainly see such deep desaturations on occasion.
Thanks for sending these.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

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

Sent: Monday, May 19, 2008 11:05 AM
To: Rich, Wade
Cc: Finer, Neil; Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: Antenatal Consent

Attached are the same graphs I sent you before (of pulse ox data) and new graphs of the infants' pulse rate for the same periods of time. There seem to be dips in pulse rate that correspond to the dips in oximeter readings. Am I correct in assuming that this points to the pulse ox data being reasonable?

Marie

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

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Monday, May 19, 2008 10:24 AM
To: Gantz, Marie
Cc: Finer, Neil
Subject: RE: Antenatal Consent

Yes, it is the only way we have of knowing if the data is valid or not.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, May 19, 2008 7:23 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

I do have the pulse rate. Do you want me to try to incorporate that into the graph as well?

-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Monday, May 19, 2008 10:19 AM
To: Gantz, Marie
Subject: RE: Antenatal Consent

We did, and I responded that we need to see the Pulse Rate to make sense of them. Do you have that data?
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, May 19, 2008 7:17 AM
To: Rich, Wade
Subject: RE: Antenatal Consent

Hi Wade,

Sorry it's taken me so long to get back to you. I was at PAS and then last week I was trying to catch up from being at PAS. I don't know that we ever did look at whether moms who delivered multiples were more likely to consent. If you want me to look into that, please let me know how you want to go about it. For example, do you want to look at only those moms who were approached for consent, those who delivered in the window, etc.?

Did you ever get the chance to look at the pulse ox graphs I sent you before PAS for those couple of kids from UNM? Please let me know what you think.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Friday, May 02, 2008 10:58 AM
To: Gantz, Marie
Subject: Antenatal Consent

Hi Marie,
Did we ever look at whether Moms who delivered multips were more likely to consent? I do not see it amongst our emails or in my presentation.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, March 08, 2007 11:37 AM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

I looked into the multiple birth issue, and it turns out that the form instructions seem slightly conflicting. On the ANT01 itself, the section for infant data (including birth number) says "This section to be filled out when the infant is born within the window." However, the MOP states the following:

"When not delivered in the window: For the SUPP01 form in the DE system, the birth order number field can be left blank along with the date of birth, Network Number and Enrolled in Study fields. For the ANT01 form, the birth order number is really the fetus number and will have a value for every entry in the log."

From looking at the data, it appears that the birth number was filled out for infants who were born in the window or out of the window, but not necessarily filled out for the other pregnancy outcomes (discharge, transfer, stillbirth, IUFD). If we look at just infants born in the window (according to the ANT02) there is a multiple pregnancy rate of

10% (47/452) and multiples make up 20% of all infants (103/508). These numbers may still seem low, however, among SUPPORT enrollees, the multiple pregnancy rate is only 15% and multiples make up 27% of the infants.

Also, there is a new wrinkle in the data you asked for. Delivered in window is only being reported on the ANT02 if the mother is approached for consent (not sure why that's the case, but it is). Given that fact, I would recommend using pregnancy outcome from the ANT01. Is that OK with you?

Thanks,
Marie

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

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 6:19 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

That gives us a numerator (# of enrolled babies), but the denominator(total # of babies delivered), still escapes us. Right?

Wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, March 07, 2007 2:53 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

I just realized I was wrong -- the ANT01 does link the antenatal consent mothers to the SUPPORT babies. I will get you the numbers you asked for tomorrow morning.

Marie

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

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 12:45 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

That is certainly a good option if it is possible.
Tx.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, March 07, 2007 9:38 AM
To: Wade Rich
Cc: Neil Finer
Subject: RE: Antenatal Consent

Hi Wade,

Unfortunately, there is no ID to link the records from SUPPORT to the Antenatal consent data (SUPPORT uses the usual network ID, but Antenatal consent has a separate "screening ID"). I think the best I could do is to look at the number of infants (and number of moms) enrolled at each center since they started participating in the Antenatal consent secondary.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, March 07, 2007 12:33 PM
To: Gantz, Marie
Cc: Neil Finer
Subject: RE: Antenatal Consent

Marie,

Do we have a way of knowing how many babies these 1249 moms had, and of those how many were enrolled ?

Wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, March 06, 2007 3:37 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

Here are the frequencies from ANT02, totals and by center. I also printed out the "other" reasons that mothers were not approached for consent, by center. Let me know what else you need.

Marie

Marie Gantz, Ph.D.

Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, March 01, 2007 4:22 PM
To: Gantz, Marie
Subject: RE: Antenatal Consent

Well, first blush I need to look at the answers to Ante02. Is it possible to just get them as percentages as a first look? I would like to look at that overall and by center, to see if someone is being more successful and why.
wade

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, March 01, 2007 1:09 PM
To: Wade Rich
Subject: RE: Antenatal Consent

Hi Wade,

Just let me know what you need, and I will get it for you. Call or email me -- whatever works best for you.

Marie

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

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, March 01, 2007 3:50 PM
To: Gantz, Marie
Subject: Antenatal Consent

Hi Marie,
I need to start gathering data for my talk in April to ACRP re: Antenatal Consent. I am not doing a final obviously, just presenting what we are learning so far. I know you guys are "pre-SPR", so let me know when I can get a word in edgewise and can get the data we have so far.
Tx.
wade

From: Zaterka-Baxter, Kristin
To: nxs5@cwru.edu; Nancy.Miller@UTSouthwestern.edu; melissa.leps@utsouthwestern.edu; ae5357@wayne.edu; bbillian@wayne.edu; ellen_hale@oz.ped.emory.edu; grisbyca@email.uc.edu; ldw@iupui.edu; monica.konstantino@yale.edu; ahensman@wihri.org; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Georgia.E.McDavid@uth.tmc.edu; foy00004@mc.duke.edu; bmackinnon@tufts-nemc.org; karen-johnson@uiowa.edu; karen.osborne@hsc.utah.edu; CBackstrom@salud.unm.edu; rohls@unm.edu; michelle_tidwell@oz.ped.emory.edu; Shirley Cosby
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade
Subject: NICHD NRN Masimo Rep (SUPPORT)
Date: Tuesday, May 13, 2008 1:18:10 PM

Dear all,

Valerie Begnoche is the clinical research coordinator for Masimo Corp who will be handling Support study oximeter questions/repairs. Dr. Sayre(b) (6) . If you have any questions or concerns regarding the study oximeters please contact Valerie (see below for her contact info):

Please note I have inquired about the oximeters sent back from NM and Emory already and will forward that reply.

Thanks,
Kris

Valerie Begnoche
Clinical Research Coordinator
Masimo Corp.
P:949-297-7341
F: 949-297-7398

From: Zaterka-Baxter, Kristin
To: Michelle Tidwell
Cc: Ellen Hale; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Rich, Wade; Gantz, Marie; Das, Abhik
Subject: SUPPORT study Masimos
Date: Monday, May 12, 2008 9:11:29 AM

Hi Michelle,

There is an RMA form posted on the NRN website under the Support study that will need to be filled out and Masimo will need to be called to give you an "RMA" number (phone number on form). This form and the two malfunctioning orange oximeters will need to be sent back to them for repair (address on the RMA). Once you've called and received the RMA number, please send me an email along with Marybeth Sayre (msayre@masimo.com), our rep at Masimo and include that RMA number and a brief description of the problem.

In the mean time, I'll locate 4 orange oximeters to send you. They will go out today for delivery tomorrow (Tuesday); do you still want them to go to Ellen's home or the office?

Thanks much and please let me know if you have any questions about this at all.
Kris

From: Michelle Tidwell [mailto:Michelle_Tidwell@oz.ped.emory.edu]
Sent: Saturday, May 10, 2008 1:34 PM
To: Zaterka-Baxter, Kristin
Cc: Ellen Hale
Subject: SUPPORT study Masimos

Hi Kris,

Hope you are doing well and having a wonderful weekend!

We are having some pulse oximeter issues... Two of our monitors (on twins no less) keep shutting off. The battery on one handheld appears to be completely dead and not charging. What do we need to do with these monitors?

Also, could you please have two more orange monitors sent to Ellen's house on Monday? With these two monitors out of commission, we only have 2 orange monitors not in use and we have 3 people consented.

Thanks!!!

Michelle

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899(b) (6) pager

From: Huitema, Carolyn Petrie
To: Angelita Hensman
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; [StatEpi] Neonatal Statisticians; [StatEpi] Neonatal Programmers; Zaterka-Baxter, Kristin; Das, Abhik; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; Georgia E McDavid; linda_reubens@urmc.rochester.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; wrich@ucsd.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; Roy.Heyne@utsouthwestern.edu; vphillips@peds.uab.edu; Brenda.H.Morris@uth.tmc.edu; vanmeurs@leland.stanford.edu; Abbot Laptook; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; Michael Cotten; Bell, Edward; Johnson, Karen; Kristi Watterberg; Roger Faix; Conra Backstrom; bradley.yoder@hsc.utah.edu; ira_adams-chapman@oz.ped.emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichjj@email.uc.edu; drfjcmd@aol.com; mgfuller@ucsd.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; Jackie.Hickman@Childrens.com; bss5@cwru.edu; lohme001@mc.duke.edu; Patricia.W.Evans@uth.tmc.edu; Kimberly.Yolton@cchmc.org; Sharon.Wright@uth.tmc.edu; ldw@iupui.edu; dhwilson@iupui.edu; Karen Osborne RN; Mackinnon, Brenda; Kennedy, Kathleen A; Katherine A Foy; melissa.leps@utsouthwestern.edu; Bara, Rebecca; bbillian@wayne.edu; Elizabeth Billian
Subject: RE: Changes to GDB, Physiologic Definition of BPD, SUPPORT and EOS
Date: Thursday, May 08, 2008 12:55:17 PM

Hi All-

No problem with RTI programming the form to be used for babies born after May 1st, 2008.
Per Dr. Stoll I will revise the Technical Memo and send out shortly.

-Carolyn

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, May 08, 2008 12:31 PM
To: Huitema, Carolyn Petrie
Cc: Rosemary (NIH/NICHD) [E] Higgins; archerst@mail.nih.gov; [StatEpi] Neonatal Statisticians; [StatEpi] Neonatal Programmers; Zaterka-Baxter, Kristin; Das, Abhik; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; Georgia E McDavid; linda_reubens@urmc.rochester.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; wrich@ucsd.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; Roy.Heyne@utsouthwestern.edu; vphillips@peds.uab.edu; Brenda.H.Morris@uth.tmc.edu; vanmeurs@leland.stanford.edu; Abbot Laptook; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; Michael Cotten; Bell, Edward; Johnson, Karen; Kristi Watterberg; Roger Faix; Conra Backstrom; bradley.yoder@hsc.utah.edu; ira_adams-chapman@oz.ped.emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6) ; mgfuller@ucsd.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; Jackie.Hickman@Childrens.com; bss5@cwru.edu; lohme001@mc.duke.edu; Patricia.W.Evans@uth.tmc.edu; Kimberly.Yolton@cchmc.org; Sharon.Wright@uth.tmc.edu; ldw@iupui.edu; dhwilson@iupui.edu; Karen Osborne RN; Mackinnon, Brenda; Kennedy, Kathleen A; Katherine A Foy; melissa.leps@utsouthwestern.edu; Bara, Rebecca; bbillian@wayne.edu; Elizabeth Billian
Subject: RE: Changes to GDB, Physiologic Definition of BPD, SUPPORT and EOS

Hi Carolyn,

Could this be changed to "babies **born** after May 1st" rather than "eligible for the physiologic exam after May 1st"? This gives us some time to submit to the IRB before the infant reaches 36 weeks. This update was sent out on April 30th to begin on May 1st!! We still need to get IRB approval and will not be able to use the updated NG07 form until it has been approved. Brown cannot get retrospective IRB approval for prospective studies. I'm not sure if any other Centers will have the same problem. Centers should have a reasonable amount of time to get IRB approval (if needed) and implement changes/updates sent out by RTI.

Thanks
Angelita

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Wednesday, April 30, 2008 8:28 PM
To: Angelita Hensman; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; Georgia E McDavid; linda_reubens@urmc.rochester.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; wrich@ucsd.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; Roy.Heyne@utsouthwestern.edu; vphillips@peds.uab.edu; Brenda.H.Morris@uth.tmc.edu; vanmeurs@leland.stanford.edu; Abbot Laptook; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; Michael Cotten; Bell, Edward; Johnson, Karen; Kristi Watterberg; Roger Faix; Conra Backstrom; bradley.yoder@hsc.utah.edu; ira_adams-chapman@oz.ped.emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichjj@email.uc.edu; (b) (6) mgfuller@ucsd.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; Jackie.Hickman@Childrens.com; bss5@cwru.edu; lohme001@mc.duke.edu; Patricia.W.Evans@uth.tmc.edu; Kimberly.Yolton@cchmc.org; Sharon.Wright@uth.tmc.edu; ldw@iupui.edu; dhwilson@iupui.edu; Karen Osborne RN; Mackinnon, Brenda; Kennedy, Kathleen A; Katherine A Foy; melissa.leps@utsouthwestern.edu; Bara, Rebecca; bbillian@wayne.edu; Elizabeth Billian
Cc: Rosemary (NIH/NICHD) [E] Higgins; archerst@mail.nih.gov; [StatEpi] Neonatal Statisticians; [StatEpi] Neonatal Programmers; Zaterka-Baxter, Kristin; Das, Abhik; Huitema, Carolyn Petrie
Subject: Changes to GDB, Physiologic Definition of BPD, SUPPORT and EOS

Dear All-

Please find attached to this email ***Technical Memo PHY5, GDB22, SUP14, EOS07*** along with revised, with highlighted changes to the:

- ***GDB Manual (May 1, 2008)***
- ***NG07 (May 1, 2008)***

Clean, revised forms will be posted to the website. Please hold keying the May 1, 2008 version of the NG07 until available in the DMS.

Physiologic Definition of BPD

The stand alone Physiologic Definition of Bronchopulmonary Dysplasia (BPD) study will become a subset of the GDB on May 1, 2008, per the decision of the Steering Committee at the January 2008 meeting. Data forms created for the Physiologic Definition of BPD (PHY01 and PHY02) will be used as worksheets for the revised NG07 and only entered into the data management system (DMS) when specified as necessary for individual studies.

Infants that are 36 wks PMA and eligible for challenge before May 1, 2008 should complete the

current PHY01 and PHY02 forms and NG07 form version date (January 1, 2006. Infants 36 wks PMA and eligible for challenge after May 1, 2008 are no longer required to enter the PHY01 and PHY02 forms and should complete the NG07 form version date May 1, 2008.

The following questions have been added on the May 1, 2008 version of the GDB study Respiratory Support form (NG07) to document whether or not an infant has BPD using the physiologic definition of BPD.

1. Is the infant eligible for the physiologic evaluation? Y N

If YES to question C.1

a. Was the evaluation performed? Y N

If YES to question C.1.a

b. Date of evaluation __ __ / __ __ / __ __ __ __
Month Day Year

c. Actual FiO2 being delivered at time of challenge For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field. __ . __ __

d. If on nasal cannula at time of challenge, record flow rate __ . __ __ __ *LPM*

e. Did the patient pass the evaluation? Y N

If NO to question C.1.a

f. If patient was eligible and evaluation not done, code reason.

1= Increased FiO2
2= Increased respiratory support (cpap or vent)
3= Instability (including Surgery/Sepsis)
4 = Parent/Physician Refusal
6 = Weaned to room air on/before day of evaluation
9 = Other- explain

SUPPORT Study

The physiologic evaluation for BPD will be completed on eligible SUPPORT study infants. The results of the evaluation will be recorded on the revised NG07. In addition to the NG07 data, the PHY01 and PHY02 forms will continue to be entered into the DMS for SUPPORT patients whenever section **C. Physiologic Evaluation** on the new NG07 is required to be completed.

EOS Study

Infants enrolled in the EOS study, outside of the GDB criteria will NOT have the physiologic definition of BPD performed for the purposes of the EOS study. Infants outside of the GDB criteria (a gestational age greater than or equal to 29 week and weighing 1001-1500g) will continue to have other relevant GDB data collected.

Thank you,
Carolyn Huitema

From: Barbara Stoll
To: Angelita Hensman
Cc: Huitema, Carolyn Petrie; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; [StatEpi] Neonatal Statisticians; [StatEpi] Neonatal Programmers; Zaterka-Baxter, Kristin; Das, Abhik; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; Georgia E McDavid; linda_reubens@urmc.rochester.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; wrich@ucsd.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; Roy.Heyne@UTSouthwestern.edu; vphillips@peds.uab.edu; Brenda.H.Morris@uth.tmc.edu; vanmeurs@leland.stanford.edu; Abbot Laptook; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; Michael Cotten; Bell, Edward; Johnson, Karen; Kristi Watterberg; Roger Faix; Conra Backstrom; bradley.yoder@hsc.utah.edu; ira_adams-chapman@oz.ped.emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; yvaucher@ucsd.edu; golds005@mc.duke.edu; gary_myers@urmc.rochester.edu; Betty Vohr; adusick@iupui.edu; steichji@email.uc.edu; (b) (6) mgfuller@ucsd.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; Jackie.Hickman@childrens.com; bss5@cwru.edu; lohme001@mc.duke.edu; Patricia.W.Evans@uth.tmc.edu; Kimberly.Yolton@cchmc.org; Sharon.Wright@uth.tmc.edu; ldw@iupui.edu; dhwilson@iupui.edu; Karen Osborne RN; Mackinnon, Brenda; Kennedy, Kathleen A; Katherine A Foy; melissa.leps@UTSouthwestern.edu; Bara, Rebecca; bbillian@wayne.edu; Elizabeth Billian
Subject: Re: Changes to GDB, Physiologic Definition of BPD, SUPPORT and EOS
Date: Thursday, May 08, 2008 12:42:13 PM

AOK with me
BJS"**Angelita Hensman" <AHensman@wihri.org> writes:**

Hi Carolyn!

Could this be changed to "babies **born** after May 1st" rather than "eligible [redacted] physiologic exam after May 1st"? This gives us some time to submit to the [redacted] before the infant reaches 36 weeks. This update was sent out on April 30th to begin on May 1st. We still need to get IRB approval and will not be able to use the updated NG07 form until it has been approved. Brown cannot get [redacted] IRB approval for prospective studies. I'm not sure if any other Centers will have this same problem. Centers should have a reasonable amount of time to get [redacted] approval (if needed) and implement changes/updates sent out by RTI.

Thanks
Angelita

From: Huitema, Carolyn Petrie [mailto:petrie@rti.org]
Sent: Wednesday, April 30, 2008 8:28 PM
To: Angelita Hensman; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; Georgia E McDavid; linda_reubens@urmc.rochester.edu; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@UTSouthwestern.edu; Nancy Newman; risa.demetrio@sharp.com; jyhall@stanford.edu; kathy.arnell@sharp.com; wrich@ucsd.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; Roy.Heyne@utsouthwestern.edu; vphillips@peds.uab.edu; Brenda.H.Morris@uth.tmc.edu; vanmeurs@leland.stanford.edu; Abbot Laptook; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; jone.tyson@uth.tmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan;

[redacted]

Dear All:

Please find attached to this email *Technical Memo PHY5, GDB22, SUP14, EOS* [redacted] with revised, with highlighted changes to the:

- *GDB Manual (May 1, 2008)*
- *NG07 (May 1, 2008)*

Clean revised forms will be posted to the website. Please hold keying the May 1, 2008 version of the NG07 until available in the DMS.

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Infants that are ≤6 wks PMA and eligible for challenge before May 1, 2008 should complete the current PHY01 and PHY02 forms and NG07 form version date January 1, 2006. Infants ≤6 wks PMA and eligible for challenge after May 1, 2008 are no longer required to enter the [redacted]

PHY02 forms and should complete the NG07 form version date May 1, 2008.

The following questions have been added on the May 1, 2008 version of the GDB Study R... Support form (NG07) to document whether or not an infant has BPD using the physiologic definition of BPD.

1. Is the infant eligible for the physiologic evaluation? Y N

If YES to question C1:

a. Was the evaluation performed? Y N

If YES to question C1a:

b. Date of evaluation / /

Month Day Year

c. Actual FIO2 being delivered at time of challenge. For infants receiving blended supplemental oxygen via nasal cannula, record the blend in this field.

d. If on nasal cannula at time of challenge, record flow rate LPM

e. Did the patient pass the evaluation? Y N

If NO to question C1a:

f. If patient was eligible and evaluation not done, code reason.

1 = Increased FIO2 4 = Parent/Physician Refusal

2 = Increased respiratory support (cpap or vent) 6 = Weaned to room air on/before day of evaluation

3 = Instability (including Surgery/Sepsis) 9 = Other, explain

SUPPORT Study

The physiologic evaluation for BPD will be completed on eligible SUPPORT study infants. The results of the evaluation will be recorded on the revised NG07. In addition to the NG07 data, the PHY... PHY02 forms will continue to be entered into the DMS for SUPPORT patients whenever s... Physiologic Evaluation on the new NG07 is required to be completed.

EOS Study

[redacted]

[redacted]

[redacted]

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics
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2015 Uppergate Dr
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Office: 404-727-2456 Fax: 404-727-5737
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From: Tate, Patti L
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org
Subject: neonatal death in the Support Study
Date: Tuesday, May 06, 2008 11:04:51 AM

PI: Kathleen Kennedy, MD
Study: Support Study
Date: (b) (6) @[redacted]
This patient was a 25 5/7 week gestation premature infant weighing 885 grams at birth. Apgars were 2, 5 at 1 minute and 5 minutes respectively with routine delivery room care including O2, bag mask ventilation, intubation and surfactant. Informed consented to the Support Study was obtained prior to delivery and the infant was randomized to the Early CPAP arm of the study enrolled at delivery. Prior to DOL 7 this infant had done well requiring only moderate support and 21% O2. On DOL 7 the infant's CXR showed atelectasis of the left lung and probably the RUL. The CBG was 7.18/65/25/24 and the rate was increased on the ventilator to 50 and positioned to expand the left lung. The repeat CXR showed expansion of the left lung but atelectasis of the right lung and the O2 requirement increased and secretions were changing. Blood cultures were drawn and a TA was also done. Anitbiotics were started. The infant became progressively worse and didn't respond to changes in ventilation, NaHCO3 (for metabolic acidosis), pressure support or volume support for hypotension. The patient coded requiring chest compressions and multiple doses of Epinephrine. The infant was pronounced dead at 1743. COD presumed sepsis (TA initial report of gram negative rods) and extreme prematurity. This event wasn't caused by the study. The parents haven't decided on an autopsy yet. A medwatch to follow.
Thanks and have a great day. Patti

From: ehale@emory.edu
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT eye exam
Date: Thursday, May 01, 2008 1:59:31 PM

Rose,

We finally were able to get an eye exam from the private MD for (b) (6) and outcome is mature.

Ellen

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: Das, Abhik; Fuller, Martha
Subject: RE: SUPPORT
Date: Tuesday, April 29, 2008 6:30:26 PM

(b) (6) – unable to reach mom to determine if f/u eye exam has been done somewhere else; coded as lost to FU at 55 weeks – data entry corrected.
(b) (6) – had 2 consecutive zone 3 exams but were entered incorrectly in the computer. This has been corrected.
(b) (6) – had difficult time getting in touch with family due to change of address and/or custody. Coded final acute status as lost to FU at 55 weeks since parent/legal guardian reported no follow up eye exam after discharge however they are willing to make an appt to have the baby's eyes checked. Will follow on them and make necessary adjustment to the data entry when it happens.
(b) (6) – has been rescheduled several times and is currently scheduled to come on 5/16/08 for the 18 month FU visit.

Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 25, 2008 10:52 AM
To: wacarlo@uab.edu; Monica Collins; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: Das, Abhik; Fuller, Martha
Subject: SUPPORT

Here is a list of missing primary and secondary outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the hard work!!! THASNK FOR THE EXCELLENT RECRUITMENT!!!

Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	SUPP10 Q:'Final acute status lost to FU at 55 weeks'=Y but infant *does* have final ROP status entered.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
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Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From:	Zaterka-Baxter, Kristin
To:	Charlene Thornton
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; nfiner@pedsmail.ucsd.edu; Rich, Wade; Gantz, Marie
Subject:	RE: NeOPRoM
Date:	Tuesday, April 29, 2008 1:39:19 PM
Attachments:	SupportDSMCRoster_Current_20071127.pdf SupportDSMCMinutes20071211.pdf PresentationSeaTac (4_2a).ppt Copy of SUPPORT0408.xls

Hi Charlene,
Attached are the documents and updated data (updates highlighted in yellow) you requested with two caveats:

1. I can not verify the answers listed for the two questions I sent in the previous email re. '*% of anticipated No.*' and '*anticipated recruitment*' until clarification is received regarding the details of the questions.
2. Please understand that the data from the imbedded secondary study *'Antenatal Consent'* i.e. the number of women screened, consented, and enrolled (presentation attached), represent only the data from those enrolled to the *secondary* and only up to the time of the presentation. It does not include *all* those enrolled in the main Support trial.

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

From: Charlene Thornton [mailto:cthornton@ctc.usyd.edu.au]
Sent: Monday, April 14, 2008 4:55 PM
To: 'Neil Finer; Zaterka-Baxter, Kristin
Subject: FW: NeOPRoM

Dear Neil and Kris

Please find attached a summary of progress so far for your trial.

As previously mentioned - a report on each trial's progress will be emailed to all collaborators prior to the NeOProM collaborators meeting in May at PAS 2008. The aim of this report is to save time on the day of the collaborator's meeting for issues other than recruitment and progress updates.

I am emailing this to you for you to confirm the details herein. If there are any components of this information which you do not want to make available to the other collaborators, please indicate so on the spreadsheet. Similiarily, if you find any errors, please correct. If there are any fields left blank, can they please be filled if able to be.

The summary will be presented in a format more condusive to easy perusal for the official document, so please do not worry about any formatting issues at this time.

If you have any queries or concerns regarding this, please do not hesitate to contact either myself, or Lisa Askie.

Thanking you for your time and committment to this collaboration

Charlene Thornton

NeOProM

NICHD Neonatal Research Network DSMC Membership Roster 11/07/07

Gordon Avery, MD, PhD ***(DSMC Chair)***
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4655 S 36th St, # B-2
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e-mail: (b) (6)

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Michael G. Ross, M.D., M.P.H.
Specialty: High-risk pregnancy and maternal-fetal medicine.
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Tel: (310) 222-3544
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Shrikant Bangdiwala , PhD
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Research Professor Biostatistics
School of Public Health
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Chapel Hill, North Carolina 27514-4145
Phone: 919-962-3266
Fax: 919-962-3265
Email: kant@unc.edu

NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

Merran A. Thomson, MD
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Department of Paediatrics and Neonatal Medicine
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London W12 0HS (UK)
Telephone: +44 208 383 3270,
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Marilee C. Allen, MD
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Carol J. Blaisdell, M.D.
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Medical Officer; Lung Developmental Biology and Pediatric Pulmonary Diseases
Division of Lung Diseases, NHLBI/NIH
(301) 435-0222 phone

(301) 480-3557 fax
blaisdellcj@nhlbi.nih.gov

FINAL (February 5, 2008)

NEONATAL RESEARCH NETWORK
DATA SAFETY AND MONITORING COMMITTEE
MINUTES

December 11, 2007

The Data Safety and Monitoring Committee for the Neonatal Research Network met via conference call on December 11, 2007 to review the second interim analysis of the ***SUPPORT Trial.*** The DSMC members in attendance for this session were Drs. Avery (Chair), Boyle, Gleason, Willinger, Clemons, Ross, Thomson, Allen and Blaisdell. Drs. Das and Gantz and Ms. Zaterka-Baxter from the data center were also present.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birthweight Infants

Dr. Das presented a summary of the background, primary outcomes, eligibility, recruitment and interim analysis methods for the Support Trial. He then continued to present study data on enrollment, compliance in oxygen saturations, primary outcomes, secondary outcomes, adverse events and protocol deviations at 50% enrollment and status.

After discussion of all data presented, the DSMC agreed that no significant safety or efficacy issues were apparent, and recommended that the study should continue as planned. However, they continue to express some concern at the slower than expected pace of recruitment into the trial and continued to note the need for monitoring the degree of separation between the high and low oxygen groups in the oxygen saturation arm of the trial. In addition, the committee voiced concern about the seemingly frequent use of High flow nasal cannula in the first 14 days for infants assigned to CPAP.

Addendum to the DCMS Minutes: After discussion of the Hot Topics in Neonatology Presentation "Oxygen control: not easy but worth the effort!" by Dr. Jay Goldsmith during the January 11, 2008 NICHD NRN Steering Committee meeting, Dr. Higgins contacted the Pediatrix Medical Group for further clarification of the data. An addendum with this additional information was presented to the DSMC on January 30, 2008. At this time the DSMC was informed of the plan to follow our Support study subjects for rate of PDA (NEC is already being followed). The general consensus after review was that the SUPPORT Trial might add some light to the issues reported and that the DSMC had no further concerns.

Pre-screening and Antenatal Informed Consent for Neonatal Trials: *A Research Conundrum*

Wade Rich BSHS, RRT, CCRC

RTI INTERNATIONAL

Antenatal Consent Trial - NRN

- Secondary to the SUPPORT Trial
- Based on input from study coordinators regarding time/effort involved in enrollment
- Target is 50 infants who delivered in the window per center

Primary Goals

- **Average number of attempts to present the study**
- **Average length of time it takes to obtain an answer regarding enrollment**
- **To determine the number of mothers that must be approached for consent to yield one enrolled subject**

Primary Goals

- **To determine reasons for failure to enroll consented newborns**

- **To determine the amount of personnel time it takes to yield one enrolled subject**

Primary Goals

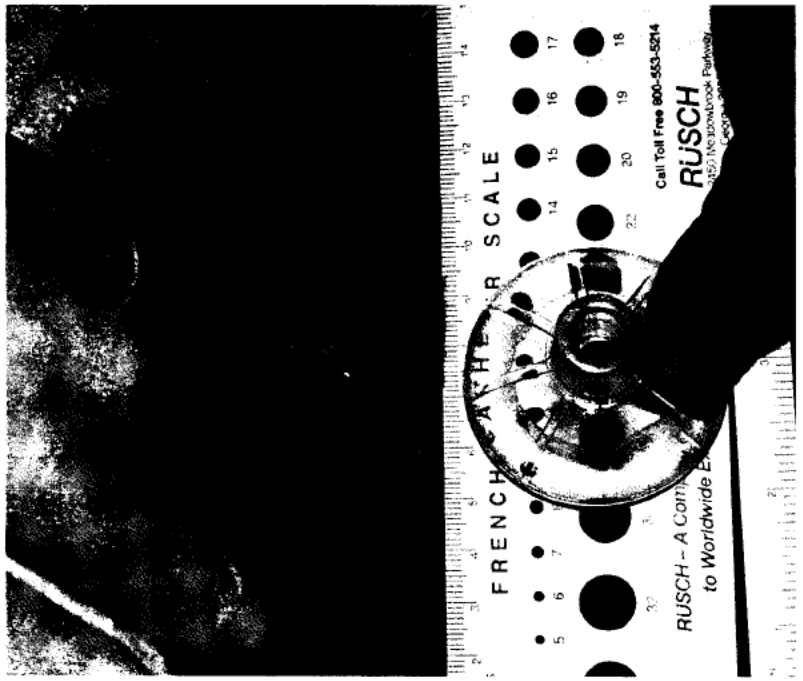
- **To determine reasons for failure to obtain consent**

- **To make recommendations regarding budgeting and antenatal recruitment practices for future neonatal studies**

The Trials

- **DR CPAP – A small pilot trial**
- **SUPPORT – A large multi-center interventional trial**
- **Antenatal Consent – A secondary to SUPPORT**

The DR CPAP Trial – 2002
Finer, et al.



- **<28 weeks Gestation (Best OB)**
- **Inborn**
- **N= 100**
- **Primary Question – Was CPAP in DR possible?**

The DR CPAP Trial – 2002
Finer, et al.

- **DR CPAP was subcommittee members (committed)**
- **Individual site visits from study PI**
- **4 of 5 centers enrolled under waiver**

DR CPAP Trial Enrollment

- **5 centers enrolled 100 subjects in 6 months**

- **Using this model, 16 centers in the main SUPPORT trial would enroll 600 babies per year, and the trial would take about 2.5 years**

Pilot Enrollment Data

- **281 infants <28wks GA infants delivered**
- **162/281 of these were screened → 120 eligible**
- **104/120 consented & enrolled**
- **Enrollment rate = *83%***

Pilot Enrollment Data

- **There were 281 infants of less than 28 weeks who delivered in the study hospitals during the period of the study.** Did not Deliver? Transferred?
- **Of whom 162 infants were screened by study personnel.** We assumed incentive would increase this.
- **Forty-two were determined to be ineligible by the study criteria.** Includes "out of window"
- **104 infants were consented of the 126 eligible patients, for an enrollment rate of *83%*." Were there 239 eligible ?**

The Main Trial - SUPPORT

- **Support trial was based on the DR CPAP model, using data from the pilot study as a benchmark**
- **Startup was not "shotgun"; covered over one year**
- **All centers required an informed consent (i.e. No Waivers)**

Why Centers Did Not Enroll Under Waiver

- **Studies which involve treatment in the delivery room have historically been either consented antenatally or have functioned under a *waiver of consent* as established in the Code of Federal Regulations**

45 CFR 46.116[d]

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration;

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

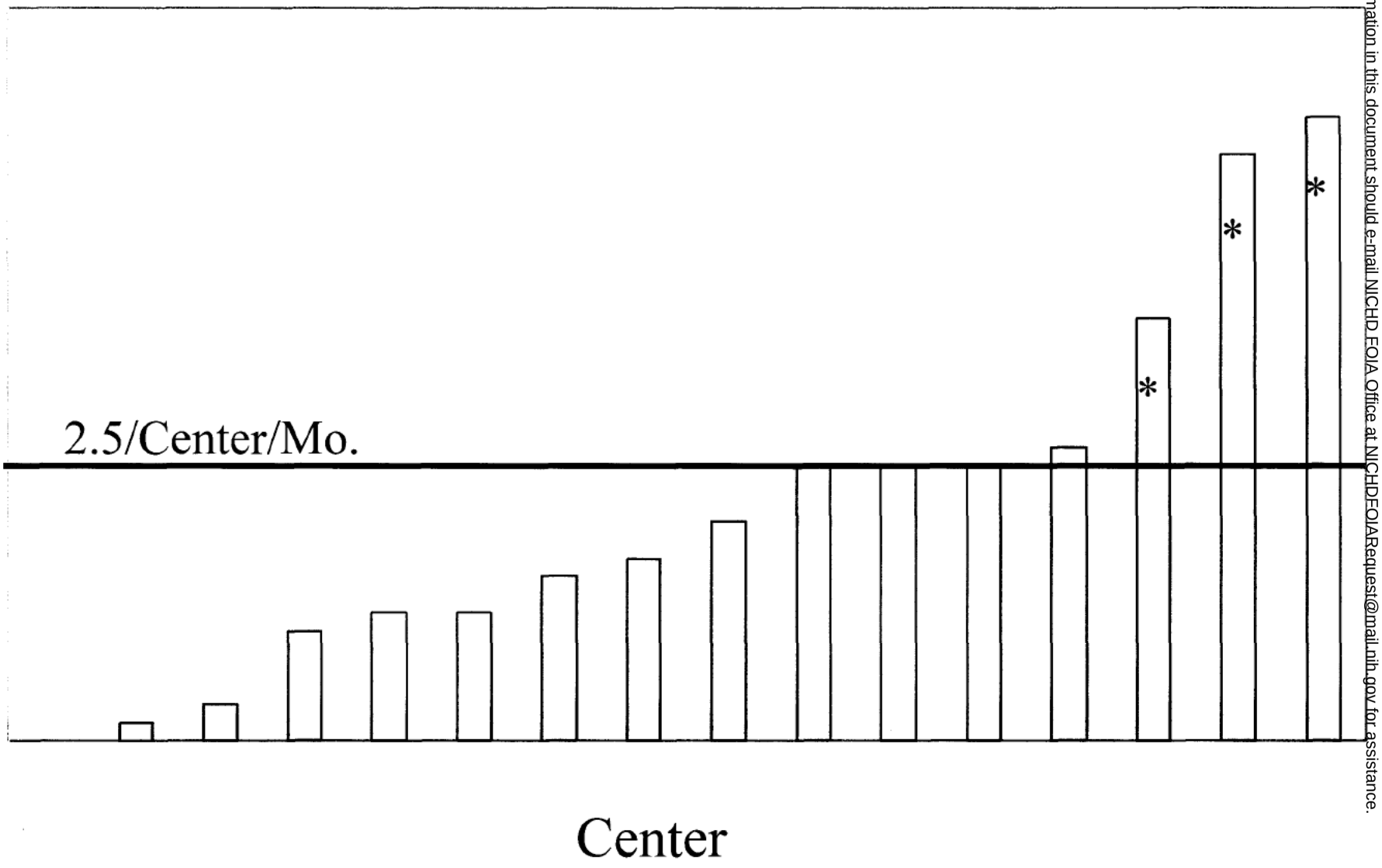
SUPPORT – The Primary Trial

- **24 – 27 6/7 GA - 4 week enrollment window**
- **Target enrollment = 1310**
- **Pool of Candidates (Delivered) = 1100/year**
- **Projected enrollment 33 to 50% of those eligible → or ~ 36/month or 2+/center/month**
- **Estimated time to completion ~ 3 years**

The 6 month Report Card

- **Averaging 2 enrollments per center per month**
- **Centers reporting difficulty with complexity of trial**
- **Coordinators describing lengthy process for obtaining consent**

Enrollment Distribution – 6 mos



Why We Can't Enroll

- **"Our IRB won't let us talk to moms in labor"**
- **"The consent requires multiple visits – ↑Time"**
- **"Moms are already overwhelmed by other studies"**
- **"We consent them, then they deliver out of the window"**

Antenatal Consent Secondary

- **Started enrolling in October 2005 or later**
- **1288 mothers have been pre-screened**
- **We have screening data from 18 centers**

Multiple Births

- **15% of pregnancies yield multiple fetuses**
- **27% of infants are from a multiple pregnancy**

What is Antenatal Consent & Pre-Screening?

Pre-Screening

Identify women hospitalized for risk of premature delivery

Antenatal Consent

Present study & ask for consent

Screening

Is infant born in window ? No congenital anomalies?

Enrollment

Randomize & start study treatments

Phase 1 - Pre-Screening

- **Coordinators and PI need to have a relationship with the perinatal service**
- **Every mother carrying a 23 week infant is not a candidate for consent**
- **Mothers move !**

Communication – OB

- **60% of the time OB permission was obtained prior to approaching a mother for consent**

- **This increases the time needed to obtain a consent, but provides a framework for two-way communication when qualifying infants arrive on Labor deck**

Neonatal Consult

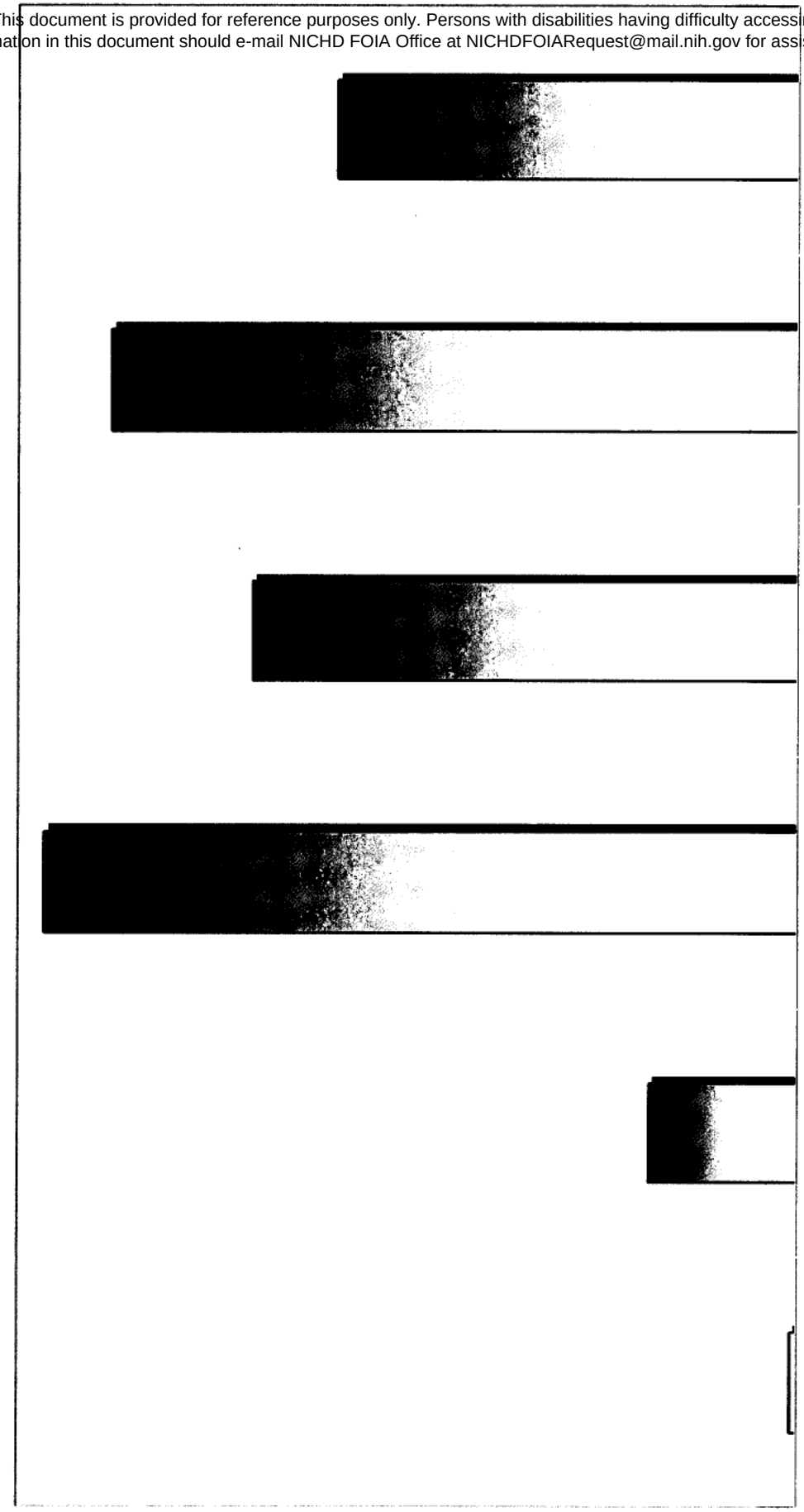
- **A neonatal consult was done on 66% of the mothers approached for this trial**
- **A mother for whom a consult was provided was significantly more likely to consent to the trial than one who did not have a consult. ($p<.02$)**
- **Centers who do consults on 100% of infants in the trial were not significantly more successful obtaining consent**

Neonatal Consult

- **In infants who had a consult, the SUPPORT trial was discussed about 1/3rd of the time**
- **Nearly 10% of infants were consented during the neonatal consult**
- **Consult becomes functional part of pre-screening process**

Phase 2 – Approaching for Consent

- When are mom's approached
- Understanding of site-specific regulations
- Determining why some mom's are not approached



Effect of GA Approached on Study

- **41% of enrollments in the 24-25 week GA stratum**
- **59% of enrollments in the 26-27 week stratum**
- **About 40% of mothers are approached after 25 weeks**
- **We do not know how long mothers were in-house prior to being approached**

Why Was Mother Not Approached ?

• Active Labor	13.3%
• Insufficient Time	15.5
• Week Night, Weekend, Holiday	8.9
• Neonatal Consult not Done	3.7
• Not notified/aware of admission	5.5
• Other	53.1 %

"Other" Reasons for Not Approaching Mother

- **Most Common –**
  - **Congenital Abnormalities**

- **Other common non-specified reasons:**
  - **Maternal illness which precluded consent**
  - **Language**

Number of Attempts

- **77 % of attempts to approach mom done by Coordinator/ Research RN**
- **77% of mothers were approached 2 or less times**
- **Range was 1-11 attempts**

Too Many Consents

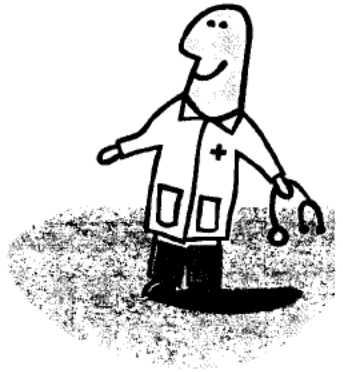
- **We were concerned that mothers who were in "Multi-Network" centers, those who were in Neonatal and Maternal NICHD networks, would overwhelm moms with consents**

- **Only 5% of screened subjects were specifically identified as being in another maternal study, and 8% in a neonatal study**

Consent Rate

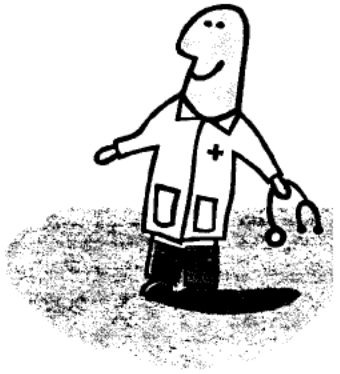
- **Of the 1288 mothers pre-screened, 1017 have current data forms indicating status of consent**

- **551 were consented , for a consent rate of 54.2 %**



What Affects Consent Rate?

- **Is the rate of consent effected by gestational age at which we approach the mother ?**
- **Is it affected by who obtains the consent?**
- **Other factors?**



What Affects Consent Rate?

- **There is a significant relationship between doing a neonatal consult and obtaining consent (P< .02)**

- **Translation: You were more likely to get a consent if a consult was done**

Phase 3 - Screening

- **Post-Consent tracking – Moved, Transferred, D/C'd, Readmitted**
- **Delivery status - Does everyone know about delivery?**
- **Equipment status - enough for multiples?**
- **Tracking through window of eligibility**

Delivery in the Study Window

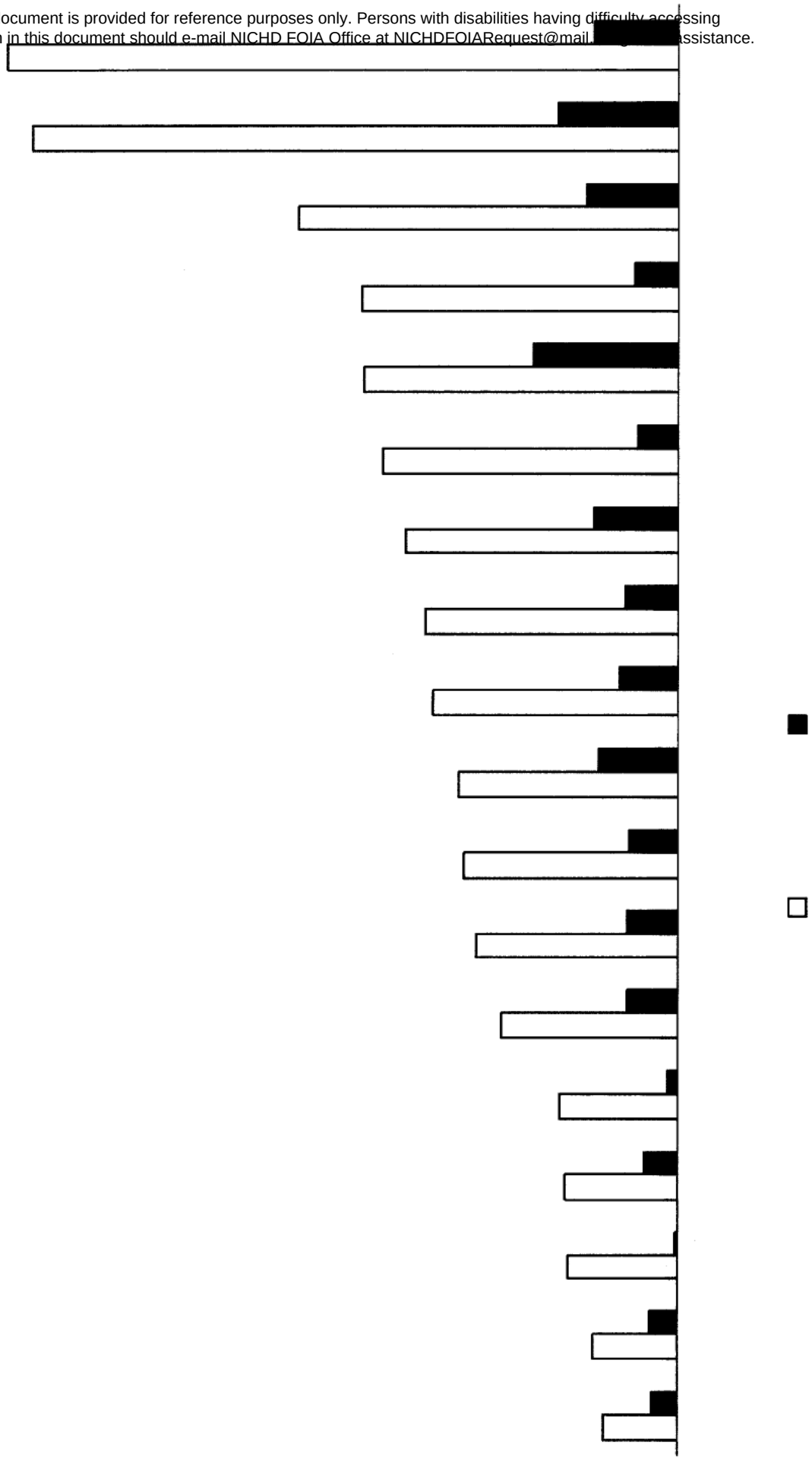
- **Only 51.5% of women who consented delivered an infant in the study window**
- **Range was 25 – 76%**
- **SUPPORT – An effective tocolytic !**

Not Delivered in the Window

- **38 % delivered out of the window in the study hospital**
- **9 % were transferred or discharged prior to delivery**
- **1 % died *in utero***

Phase 4 - Enrollment

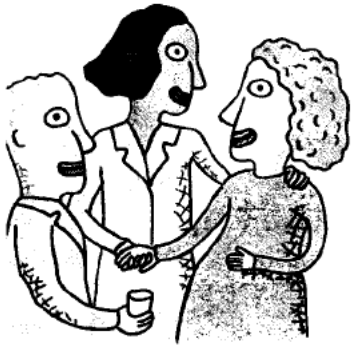
- **What was the rate of enrollment ?**
- **What factors effected that rate?**
- **Who were the most efficient enrollers ?**



When Mothers Were Approached

Gestational Age at first contact (Weeks)

Weeks	#	%
22	2	0.2
23	58	5.7
24	295	29.0
25	214	21.0
26	268	26.4
27	180	17.7



When Mothers Were Approached

The average GA at which mothers were first approached was not significantly different for those who consented and those who did not .

Too Many Consents

- **Centers who have both types of Networks in place are now 4 of the top 5 enrollers**

- **These centers approach more women, get more consults, enrolled at a higher rate, and were more likely to use <30 minutes to obtain a consent**

The Current Numbers - Overview

- **1288 moms were screened**
- **1017 were approached for consent**
- **551 agreed to allow their infants to participate**
- **289 infants and 254 moms enrolled in the trial**
- **1288/254 = 5:1 screening to enrollment ratio**

SUPPORT – Workload

Each enrolled subject required the following:

- **4 unsuccessful screenings (1-11 visits ea.) at 1.2 hour.**
- **1 successful screening (1-11visits ea.) at 1.2 hours for this subject**
- **6 hours screening/subject.**

The Bottom Line

- **In a trial with antenatal consent and a 4 week delivery window, we found that you must approach five women and spend about six hours just in the pre-enrollment process in order to enroll *one* infant in the trial .**

Limitations of the Study

- **Data was collected by coordinators**
- **We are missing the overall denominator**
- **No information regarding comparing coordinators with physicians regarding consent rates**
- **Data collection is not yet complete**

Implications

- **Studies requiring antenatal consent must budget more coordinator time for recruitment**

- **When establishing timelines for a trial, a screening to recruitment ratio of 5:1 is reasonable**

Where do we go from here?

- **How does this estimate differ from the amount of time it takes to consent for studies at/after birth? Should studies requiring antenatal consent be budgeted differently than post-natal consent studies?**

- **Are there ways to shorten the amount of time spent doing antenatal consent?**

Participating Centers

Case Western Univ.

Univ. of Texas-Dallas

Univ. of Miami

Emory University

Univ. of Cincinnati

Indiana Univ.

Brown Univ.

Wayne St. Univ.

Stanford University

Stanford University

Univ. of Alabama – Birmingham

Univ. of Texas – Houston

Duke Univ.

Yale Univ.

UCSD

Tufts Univ.

Univ. of Utah

Univ. of New Mexico

University of Iowa

NAME	SUPPORT
FUNDING SOURCE	NICHD/NHLBI
CO-ORDINATING CENTRE	NICHD Neonatal Research Network
NO. NEEDED	1310
No. RECRUITED	1024 (as of 04/25/08)
% OF REQUIRED RECRUITMENT	78%
ANTICIPATED RECRUITMENT	30/month
% OF ANTICIPATED NO.	70%
PLANNED COMPLETION OF RECRUITMENT	Mar-08
ACTUAL COMPLETION OF RECRUITMENT	May-09
DATE DUE FOR PRIMARY/IMPORTANT OUTCOMES	Due date for the primary outcomes for SUPPORT (BPD/ROP/Death) will be ~6 months after the last patient is recruited. Assessment of long-term FU outcomes are expected to be completed by May 2011-Jul 2011
RECRUITING FROM CURRENTLY	Case Western Reserve
	University of Alabama
	Brown University
	University of Cincinnatti
	Indiana University
	Emory University
	~~University of Miami~~
	Stanford Univesity
	University of Texas-Dallas
	University of Texas-houston
	Wayne State University
	Yale University
	Duke University
	~~Wake Forest University~~
	UCSD
	~~University of Rochester~~
	Tufts Medical Center
	University of Iowa
	University of Utah
	University of New Mexico
RECRUITMENT COMMENCED	Mar-05
RECRUITMENT COMPLETED	No
DSMC FORMED	Yes
DSMC MEMBERS	Please see attached document
DSMC MEETINGS HELD	Teleconference
DATES DSMC MEETINGS HELD	12/11/07 to review the second interim analysis at 50% study status
TRIAL COMPLIANCE	For compliance, we do the following 1) Create quarterly reports showing the percent of time spent in the narrow and wide target ranges, aggregated by center with the treatment groups combined to give feedback to the centers on how they are doing. 2) Create reports by treatment group for the DSMC meetings. 3) Centers enter protocol deviations for times when the infants are off the oximeters when they should be on. 4) Investigate unexplained gaps in the PO data. 5) Monitor source documentation for compliance during site monitoring visits (since 12/06, we have conducted 7 sites monitored visits).
FREQUENCY COMPLIANCE TESTED	compliance is looked at quarterly with the treatment groups combined, and at 25%, 50%, 75% of outcome attainment for the DSMC by treatment groups
SOFTWARE USED	SAS
RESULTS OF COMPLIANCE TESTING	

From: Evans, Patricia W
To: Tyson, Jon E; Kennedy, Kathleen A; Morris, Brenda H; Mcdavid, Georgia E; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wright, Sharon ; Alaniz, Nora I
Subject: RE: SUPPORT
Date: Tuesday, April 29, 2008 2:25:56 PM

From Sharon re: the infant noted below:

This is a child we've never seen. He was readmitted soon after his NICU discharge and the parents had such a bad experience, they transferred him to TCH. Last June, we talked with the mom who stated they had no interest in coming to see us despite the fact that we explained the difference between the hospital and the medical school. We've called and sent letters with no further communication on her part. I think we need to declare this child lost-to F/U and move on.

We will submit the lost-to-follow-up form for this baby.

Thank you,

Patricia W. Evans, MD
Assistant Professor of Pediatrics, Division of Neonatology
The University of Texas Medical School at Houston
713-500-5311 (office)
713-500-5794 (fax)
Patricia.W.Evans@uth.tmc.edu <mailto:Patricia.W.Evans@uth.tmc.edu> (e-mail)

Eco-Tip: Turn off the light in any unoccupied room--including your office, a conference room, or the bathroom. (from www.treehugger.com <http://www.treehugger.com/>)

From: Tyson, Jon E
Sent: Fri 4/25/2008 1:09 PM
To: Evans, Patricia W
Subject: FW: SUPPORT

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 25, 2008 10:53 AM
To: Kennedy, Kathleen A; Morris, Brenda H; Tyson, Jon E; Mcdavid, Georgia E
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Here is a list of missing primary and secondary outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the hard work!!!

Rose

CENTER

NETWORK

ROP_message

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

18

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, April 29, 2008 11:15:10 AM

Rose,
I know we have talked about this one and I am really trying to get this done. I have checked and I have entered the data on (b) (6) , hope I entered in the right place it is under regular f/u not support f/u and the other one i have entered everything except the Bayley scores which I will take care of today or tomorrow.These both had Bayley II's done instead of III's ,due to an error on our part.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 04/25/08 9:40 AM >>>
Here is a list of missing primary and secondary outcomes for SUPPORT.
Let us know how you are doing.

Thanks for all the hard work!!!

Rose

CENTER

NETWORK

FU_message

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human

Development

National Institutesof Health

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Bethesda, MD 20892

For overnight delivery use Rockville, MD 20592

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, April 28, 2008 2:36:59 PM

No, UCSD's last data transmission was 3-25-08. Jenny is going to talk to them about transmitting more often.

Marie

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

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, April 26, 2008 11:21 AM
To: Gantz, Marie
Subject: Fw: SUPPORT

Is this in the DMS?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Bridge, Renee <rbridge@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Apr 26 10:33:27 2008
Subject: RE: SUPPORT

Hi, We gained new information on patient (b) (6), so I completed the SUPP 10 with the new info. I entered all of patient (b) (6) on 3/28/2008. Hope that is the info needed. Thanks. Renee

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 4/25/2008 8:57 AM
To: Finer, Neil; Rich, Wade
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Here is a list of missing primary and secondary outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the hard work!!!

Rose

CENTER

NETWORK

ROP_message

22

(b) (6)

SUPP10 Q:'Final acute status lost to FU at 55 weeks'=Y but infant does have final ROP status entered.

22

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutesof Health

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MSC 7510

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Gantz, Marie
Subject: RE: NeOPRoM
Date: Monday, April 28, 2008 1:55:27 PM
Attachments: Copy of SUPPORT0408.xls

Just updated a few more numbers to date; please see rows highlighted in green.
Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Monday, April 28, 2008 1:42 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Das, Abhik; 'Finer, Neil'; Gantz, Marie
Subject: RE: NeOPRoM

HI all,
Below is an email from the NeOPRoM coordinator for the May PAS meeting. She sent the excel spreadsheet attached which I have updated (yellow highlights) and plan to send back to her along with the requested DSMC documents and Antenatal study presentation as approved by the SC in April. Please take a look at this information and let me know if it is appropriate to sent. I do have a question about the last item requested on the spreadsheet *"Results of Compliance Testing"*. I don't believe the release of that information was approved by the SC; please let me know how you would like us to handle this request.

Thanks,
Kris

From: Charlene Thornton [mailto:cthornton@ctc.usyd.edu.au]
Sent: Monday, April 14, 2008 4:55 PM
To: 'Neil Finer; Zaterka-Baxter, Kristin
Subject: FW: NeOPRoM

Dear Neil and Kris

Please find attached a summary of progress so far for your trial.

As previously mentioned - a report on each trial's progress will be emailed to all collaborators prior to the NeOProM collaborators meeting in May at PAS 2008. The aim of this report is to save time on the day of the collaborator's meeting for issues other than recruitment and progress updates.

I am emailing this to you for you to confirm the details herein. If there are any components of this information which you do not want to make available to the other collaborators, please indicate so on the spreadsheet. Similiarily, if you find any errors, please correct. If there are any fields left blank, can they please be filled if able to be.

The summary will be presented in a format more condusive to easy perusal for the official document, so please do not worry about any formatting issues at this time.

If you have any queries or concerns regarding this, please do not hesitate to contact either myself, or Lisa Askie.

Thanking you for your time and committment to this collaboration

Charlene Thornton
NeOProM

NAME	SUPPORT
FUNDING SOURCE	NICHD/NHLBI
CO-ORDINATING CENTRE	NICHD Neonatal Research Network
NO. NEEDED	[redacted]
No. RECRUITED	
% OF REQUIRED RECRUITMENT	
ANTICIPATED RECRUITMENT	
% OF ANTICIPATED NO.	70%
PLANNED COMPLETION OF RECRUITMENT	Mar-08
ACTUAL COMPLETION OF RECRUITMENT	May-09
DATE DUE FOR PRIMARY/IMPORTANT OUTCOMES	May-11-Jul-11
RECRUITING FROM CURRENTLY	Case Western Reserve University of Alabama Brown University University of Cincinnatti Indiana University Emory University ~~University of Miami~~ Stanford Univesity University of Texas-Dallas University of Texas-houston Wayne State University Yale University Duke University ~~Wake Forest University~~ UCSD ~~University of Rochester~~ Tufts Medical Center University of Iowa University of Utah University of New Mexico
RECRUITMENT COMMENCED	Mar-05
RECRUITMENT COMPLETED	No
DSMC FORMED	Yes
DSMC MEMBERS	Please see attached document
DSMC MEETINGS HELD	Teleconference
DATES DSMC MEETINGS HELD	12/11/07 to review the second interim analysis at 50% study status
TRIAL COMPLIANCE	For compliance, we do the following 1) Create quarterly reports showing the percent of time spent in the narrow and wide target ranges, aggregated by center with the treatment groups combined to give feedback to the centers on how they are doing. 2) Create reports by treatment group for the DSMC meetings. 3) Centers enter protocol deviations for times when the infants are off the oximeters when they should be on. 4) Investigate unexplained gaps in the PO data. 5) Monitor source documentation for compliance during site monitoring visits (since 12/06, we have conducted 7 sites monitored visits).
FREQUENCY COMPLIANCE TESTED	compliance is looked at quarterly with the treatment groups combined, and at 25%, 50%, 75% of outcome attainment for the DSMC by treatment group.
SOFTWARE USED	SAS
RESULTS OF COMPLIANCE TESTING	

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Finer, Neil; Gantz, Marie
Subject: RE: NeOPRoM
Date: Monday, April 28, 2008 1:42:07 PM
Attachments: SupportDSMCRoster_Current_20071127.pdf
SupportDSMCMinutes20071211.pdf
Copy of SUPPORT0408.xls

HI all,
Below is an email from the NeOPRoM coordinator for the May PAS meeting. She sent the excel spreadsheet attached which I have updated (yellow highlights) and plan to send back to her along with the requested DSMC documents and Antenatal study presentation as approved by the SC in April. Please take a look at this information and let me know if it is appropriate to sent. I do have a question about the last item requested on the spreadsheet *"Results of Compliance Testing"*. I don't believe the release of that information was approved by the SC; please let me know how you would like us to handle this request.

Thanks,
Kris

From: Charlene Thornton [mailto:cthornton@ctc.usyd.edu.au]
Sent: Monday, April 14, 2008 4:55 PM
To: 'Neil Finer; Zaterka-Baxter, Kristin
Subject: FW: NeOPRoM

Dear Neil and Kris

Please find attached a summary of progress so far for your trial.

As previously mentioned - a report on each trial's progress will be emailed to all collaborators prior to the NeOProM collaborators meeting in May at PAS 2008. The aim of this report is to save time on the day of the collaborator's meeting for issues other than recruitment and progress updates.

I am emailing this to you for you to confirm the details herein. If there are any components of this information which you do not want to make available to the other collaborators, please indicate so on the spreadsheet. Similiarily, if you find any errors, please correct. If there are any fields left blank, can they please be filled if able to be.

The summary will be presented in a format more condusive to easy perusal for the official document, so please do not worry about any formatting issues at this time.

If you have any queries or concerns regarding this, please do not hesitate to contact either myself, or Lisa Askie.

Thanking you for your time and committment to this collaboration

Charlene Thornton
NeOProM

NICHD Neonatal Research Network DSMC Membership Roster **11/07/07**

Gordon Avery, MD, PhD ***(DSMC Chair)***
Specialty: Neonatology, Clinical Trials
4655 S 36th St, # B-2
Arlington, VA 22206
Telephone: (703) 820-3134
Cell: (703) 405(b) (6)
e-mail: (b) (6)

Robert J. Boyle, MD
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Dept. of Pediatrics,
Division of neonatology
Room 3747, Old Medical School
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Marian Willinger, PhD
Specialty: Control of Breathing, SIDS
Pregnancy and Perinatology Branch,
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Michael G. Ross, M.D., M.P.H.
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Professor of Ob/Gyn and Public Health, UCLA School of Medicine and Public Health; Chairman, Department of Ob/Gyn.
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Phone: 919-962-3266
Fax: 919-962-3265
Email: kant@unc.edu

NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

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Hammersmith Hospital,
Du Cane Road
London W12 0HS (UK)
Telephone: +44 208 383 3270,
Fax: +44 208 764 8281
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Marilee C. Allen, MD
Specialty: Neonatology, High risk infant follow-up, Neurodevelopment
Associate Professor of Pediatrics
Department of Pediatrics/Division of Neonatology
The Johns Hopkins University School of Medicine
600 N. Wolfe St., CMSC 210
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Carol J. Blaisdell, M.D.
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Medical Officer; Lung Developmental Biology and Pediatric Pulmonary Diseases
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FINAL (February 5, 2008)

NEONATAL RESEARCH NETWORK
DATA SAFETY AND MONITORING COMMITTEE
MINUTES

December 11, 2007

The Data Safety and Monitoring Committee for the Neonatal Research Network met via conference call on December 11, 2007 to review the second interim analysis of the ***SUPPORT Trial.*** The DSMC members in attendance for this session were Drs. Avery (Chair), Boyle, Gleason, Willinger, Clemons, Ross, Thomson, Allen and Blaisdell. Drs. Das and Gantz and Ms. Zaterka-Baxter from the data center were also present.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birthweight Infants

Dr. Das presented a summary of the background, primary outcomes, eligibility, recruitment and interim analysis methods for the Support Trial. He then continued to present study data on enrollment, compliance in oxygen saturations, primary outcomes, secondary outcomes, adverse events and protocol deviations at 50% enrollment and status.

After discussion of all data presented, the DSMC agreed that no significant safety or efficacy issues were apparent, and recommended that the study should continue as planned. However, they continue to express some concern at the slower than expected pace of recruitment into the trial and continued to note the need for monitoring the degree of separation between the high and low oxygen groups in the oxygen saturation arm of the trial. In addition, the committee voiced concern about the seemingly frequent use of High flow nasal cannula in the first 14 days for infants assigned to CPAP.

Addendum to the DCMS Minutes: After discussion of the Hot Topics in Neonatology Presentation "Oxygen control: not easy but worth the effort!" by Dr. Jay Goldsmith during the January 11, 2008 NICHD NRN Steering Committee meeting, Dr. Higgins contacted the Pediatrix Medical Group for further clarification of the data. An addendum with this additional information was presented to the DSMC on January 30, 2008. At this time the DSMC was informed of the plan to follow our Support study subjects for rate of PDA (NEC is already being followed). The general consensus after review was that the SUPPORT Trial might add some light to the issues reported and that the DSMC had no further concerns.

NAME	SUPPORT
FUNDING SOURCE	NICHD/NHLBI
CO-ORDINATING CENTRE	NICHD Neonatal Research Network
NO. NEEDED	1320
No. RECRUITED	950 (February 2008)
% OF REQUIRED RECRUITMENT	72%
ANTICIPATED RECRUITMENT	37/month
% OF ANTICIPATED NO.	70%
PLANNED COMPLETION OF RECRUITMENT	Mar-08
ACTUAL COMPLETION OF RECRUITMENT	May-09
DATE DUE FOR PRIMARY/IMPORTANT OUTCOMES	May-11-Jul-11
RECRUITING FROM CURRENTLY	Case Western Reserve
	University of Alabama
	Brown University
	University of Cincinnatti
	Indiana University
	Emory University
	~~University of Miami~~
	Stanford Univesity
	University of Texas-Dallas
	University of Texas-houston
	Wayne State University
	Yale University
	Duke University
	~~Wake Forest University~~
	UCSD
	~~University of Rochester~~
	Tufts Medical Center
	University of Iowa
	University of Utah
	University of New Mexico
RECRUITMENT COMMENCED	Mar-05
RECRUITMENT COMPLETED	No
DSMC FORMED	Yes
DSMC MEMBERS	Please see attached document
DSMC MEETINGS HELD	Teleconference
DATES DSMC MEETINGS HELD	12/11/07 to review the second interim analysis at 50% study status
TRIAL COMPLIANCE	For oxygenation compliance, we do the following 1) Create quarterly reports showing the percent of time spent in the narrow and wide target ranges, aggregated by center with the treatment groups combined to give feedback to the centers on how they are doing. 2) Create reports by treatment group for the DSMC meetings. 3) Centers enter protocol deviations for times when the infants are off the oximeters when they should be on. 4) Investigate unexplained gaps in the PO data. 5) Monitor source documentation for compliance during site monitoring visits (since 12/06, we have conducted 7 sites monitored visits).
FREQUENCY COMPLIANCE TESTED	compliance is looked at quarterly with the treatment groups combined, and at 25%, 50%, 75% of outcome attainment for the DSMC by treatment group
SOFTWARE USED	SAS
RESULTS OF COMPLIANCE TESTING	

From: Billian, Elizabeth
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Sood, Beena; Shankaran, Seetha
Subject: SUPPORT
Date: Friday, April 25, 2008 3:04:44 PM

This is information on the 3 infants that have reached 50 weeks PMA:

(b) (6) had their last eye exam on 12/7/07; I have spoken to the mother twice but she still has not made an eye appointment for the twins. I was unable to contact her today but I will keep trying.
(b) (6) had her last eye exam on 3/14/08. She missed her next 2 appointments but she was seen in the office today. The form was not completed today but should be done soon.

Betty

Betty Billian, RN, BSN
Research Assistant-Neonatology
Wayne State University
Phone- 313-993-7216
Pager (b) (6)

From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg
Cc: ellen_hale@oz.ped.emory.edu; Zaterka-Baxter, Kristin; Finer, Neil; Barbara Stoll
Subject: RE: Study monitors
Date: Friday, April 25, 2008 1:29:22 PM

Sent!
Kris, we sent 312214 and 317560 via UPS for delivery at Ellen's house tomorrow.
UPS Tracking # is 4684 874 164 6
Monica

Ellen--have a great weekend!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 4/25/2008 11:56 AM
To: Cunningham, Meg; Monica Collins
Cc: ellen_hale@oz.ped.emory.edu; Zaterka-Baxter, Kristin; Finer, Neil; Barbara Stoll
Subject: RE: Study monitors

THANKS TO ALL
ROSE

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, April 25, 2008 12:55 PM
To: mcollins@peds.uab.edu
Cc: ellen_hale@oz.ped.emory.edu; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Study monitors

Hi Monica,

Below is Ellen's home address. Thanks so much!

Meg

From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
Sent: Friday, April 25, 2008 12:39 PM
To: Cunningham, Meg
Subject: Study monitors

Meg,
I sent this email to Kris yesterday afternoon but she must not have seen it. Do you know if monitors have been sent? If not, can you get 2 orange for me?

Well most of our consented SUPPORT moms have delivered and we could use a few

extra monitors. We have enough for right now but could use 2 more orange if they could be sent tomorrow to my home.

(b) (6)

home phone: 770-422-(b) (6)

Thanks,
Ellen

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, April 25, 2008 1:28:02 PM

---

thought this would make your day if this is the one she keeps requesting...

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, April 25, 2008 11:00 AM
To: Poindexter, Brenda B; Wilson, Leslie Dawn; Richard, Leslie D; Dusick, Anna M.
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Here is a list of missing primary and secondary outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the hard work!!!

Rose

CENTER

NETWORK

ROP_message

12

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

12

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592

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

From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: Das, Abhik; Fuller, Martha
Subject: RE: SUPPORT
Date: Friday, April 25, 2008 11:53:21 AM

Got it--will check with the follow-up people when Vivien gets back on Monday
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 4/25/2008 10:51 AM
To: wacarlo@uab.edu; Monica Collins; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: Das, Abhik; Fuller, Martha
Subject: SUPPORT

Here is a list of missing primary and secondary outcomes for SUPPORT. Let us know how you are doing.

Thanks for all the hard work!!! THASNK FOR THE EXCELLENT RECRUITMENT!!!

Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	SUPP10 Q:'Final acute status lost to FU at 55 weeks'=Y but infant *does* have final ROP status entered.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutesof Health
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Subject: apoE IRB approval
Date: Thursday, April 24, 2008 7:39:04 PM
Attachments: 322-99modR10.pdf

Rose,
Please, find attached our IRB approval for apoE.

Our dry spell with SUPPORT has come to an end, We now have 8 babies in SUPPORT (3 last month and 5 so far this month).

Ellen

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

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

The Emory University IRB has approved your modification entitled, "Randomized, controlled trial of induced hypothermia for hypoxic-ischemic encephalopathy in term infants".

Attached to this email is a PDF file that contains the signed modification request, stamped consent form(s), and stamped HIPAA authorization form(s). This email and the attached documents will serve as your official notification of the IRB's action. Please note that beginning in February 2008, we will send a hard copy only upon request.

Please let me know if you have any questions or concerns about this matter. Thank you.

Sarah K. Clark

Research Protocol Analyst

Institutional Review Board

Emory University

1599 Clifton Rd, 5th Floor

Atlanta, GA 30322

Direct Line: 404-712-0218

Institutional Review Board
1256 Briarcliff Road, 307-N
Atlanta, GA 30306

Phone (404) 712-0720
Fax (404) 727-1358
http://www.emory.edu/IRB

REQUEST FOR MODIFICATION

RD

Modification #: 8

Section I. Investigator Information

IRB Number 322-99	Title Randomized, controlled trial of induced hypothermia for hypoxic-ischemic encephalopathy in term infants
Principal Investigator Barbara J. Stoll, MD	Interoffice Address (Include Department, Bldg, Room or mail stop number) PO Box 26015 80 Jesse Hill, Jr. Dr. Atlanta, GA 30303
Contact Name Ellen Hale, RN	
Phone 404-616-4218	Fax 404-524-3953
Email ehale@emory.edu	

Section II. Type of Modification (Select All That Apply)

☐	Amendment	(Attach a Narrative and Supporting documentation) Amendment # _____ Date of Amendment _____
☒	New Procedures	Describe how the change affects the risk/benefit: (Attach a description of the procedures) Secondary Protocol for the Hypothermia Extended Follow-Up Study "Association of Apolipoprotein E (apoE) genotype with brain injury and neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy"
☐	Change in Study Personnel	☐ add ☐ delete ☐ change Include role of personnel, address, phone, fax, email for additions – REMEMBER, all persons on a study must have current CITI certification.
☐	Change of Site	☐ add ☐ delete ☐ modify (Attach a narrative that lists the resulting sites)
☐	Change in Enrollment	(Attach narrative justifying the change) increase #_____ decrease #_____ resulting total _____ to be enrolled
☐ ☒	Consent Change New Consent	Version Date:_____ **Highlighted changes** and **A clean copy must be attached** Date: 4/01/2008 Targeted Population: 5 children in follow-up study
☐	Advertisement	Select All that apply and attach copies of ad or announcement ☐ Newspaper Ad – Name of Paper _____ ☐ Radio Announcement – Station _____ ☐ Internet Posting - Web-site _____ ☐ Post on Clinical Trials Web site (www.emoryhealthcare.org/clinicaltrials) ☐ Television Announcement – Station _____ ☐ Flyer – Distributed where _____ ☐ Information Brochure - Distributed how _____ ☐ Other - Describe:_____ Has this ad been approved by the sponsor? ☐ Yes ☐ No ☐ N/A
☐	Clinical Investigator's Brochure	Select one: ☐ Addendum ☐ Updated ☐ New Date: Date: Date: Should consent be changed based upon this revision? ☐ Yes ☐ No
☐	Funding	☐ Add Agency Name: ☐ Delete Agency Name:

☒	Site	List all sites this amendment applies to: Emory Childern's Center and CHOA at Egleston and Hughes's Spalding
☐	Other	(e.g., Annual Report, Package Insert, General Correspondence) Describe and attach a narrative.

☒ Supporting documentation is attached. (e.g., Narrative, **highlighted consent**, form 1572, etc.) MANDATORY

PI Signature Barbara J. Stoll MD / Ellen Haller RN Date 4/4/08

Faculty Advisor (if PI is student) _____ Date _____

NARRATIVE: Please find attached the protocol, lay summary, consent, HIPAA , and COC documents for this secondary study for the Hypothermia 6-7 year Follow Up Study. The samples will be collected at the time of the study visit.

4/22 approve

Section III. IRB USE ONLY

*** Protocol expiration is not changed by the approval of this modification***

✓ The Modification has been approved.

___ The Correspondence has been acknowledged.

✓ Consent(s) and/or HIPAA Authorization dated 4/1/08 has been approved, but need to see grammar in 1st para - see post-it

___ Subjects currently enrolled must sign the new consent.

_____ Approval Date: 4/16/08 Approval Type: ___ Full ✓ Expedited

IRB Committee Member

Section below for Research Studies Performed at the Atlanta VA

Section IV. RESEARCH & DEVELOPMENT COMMITTEE USE ONLY

___ Modification has been approved by the R&D Committee

_____

R&D Committee Chair Approval Date

Emory University School of Medicine
Department of Pediatrics
Informed Consent Form

Title: "Association of Apolipoprotein E (apoE) genotype with brain injury and neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy" A Secondary Study for Extended Follow-up of the Hypothermia Trial Study

Principal Investigators: Barbara J. Stoll, M.D.
Ira Adams-Chapman, M.D., Co-PI

Sponsor: National Institute of Child Health and Human Development

Introduction/Purpose:

You are being asked to volunteer your child for a research study. The purpose of this study is to try to understand the presence of certain genes (genetic material) in your child. These genes might help your child recover more fully from his/her brain injury. The gene for apolipoprotein E (apoE) has been studied in adults. It has been linked with how people get better after they had a stroke or bleeding in the brain. Different forms of this gene have also been related to the recovery of learning and memory after some kinds of heart surgery. We want to know if the presence or absence of different types of this gene in infants might make a difference. We want to know if it makes a difference in their medical outcome after brain injury. We want to know if it makes a difference in their developmental outcome after brain injury. Your child is eligible to participate because he/she was enrolled in the study entitled "Randomized, controlled trial of induced hypothermia for hypoxic-ischemic encephalopathy in term infants." Your child is now being seen for the Extended Follow-Up of that study. Fifteen other medical centers in the U.S. are also involved in this study. This research is sponsored by the National Institute of Child Heath and Human Development (NICHD). We plan to follow about 5 children at Emory for this study.

Procedure:

There are skin cells on the inside of the mouth. The genes we want to find out about are in these skin cells. We can study these cells to find out about the body. As part of this study, a member of the research team will gently rub the inside of your child's cheek with a Q-tip. These skin cells will be rubbed onto the Q-tip (this is called a buccal swab). This will take a few seconds and should not cause any discomfort.

Risks:

There are no known risks to this procedure.

Benefits:

Taking part in this study may not directly help your child. The information obtained may help doctors to develop better ways of treating and predicting the outcomes of other newborn infants with brain injuries.

Confidentiality:

All information on you and your child will be kept private. We will use a study number rather than your child's name on study records. Your child's name and other

facts that might point to you will not appear when we show this study or publish its result. People other than those doing the study may look at study records. Agencies that make rules and policy about how research is done have the right to review these records. So do agencies that pay for the study. Those with the right to look at your records include the Emory University Institutional Review Board; Grady Research Oversight Committee (ROC); Children's Healthcare of Atlanta IRB; the Emory University Clinical Trials Office; Dr. Ricki Goldstein's lab at Duke University; The Emory University Office of Research Compliance; Research Triangle Institute (RTI); The Neonatal Research Network of the NICHD; research monitors and reviewers; data safety monitoring boards; and any government agencies who regulate the research including the U.S. Department of Health and Human Services and the Office of Human Subjects Research Protections. Records can also be opened by court order. We will keep your child's records private to the point allowed by law. We will do this even if outside review occurs.

If your child has been a patient at an Emory Healthcare facility, then they will have an Emory Healthcare medical record. If your child has never been an Emory Healthcare patient, then they will not have an Emory Health medical record and no medical record will be created for them just because they are participating in a research study.

Due to confidentiality considerations, the Emory IRB has determined that the results from following tests and procedures that are done during the research study should not be included in your child's medical record: buccal smears. The researchers will take steps to make sure that these results are not placed in any Emory Healthcare medical record that your child may have, and the results will not be made available to any other healthcare providers who may be giving them treatment. It will be up to you to let your healthcare providers know that your child is in a clinical trial. These results will be kept by the researchers in a research record.

Results from other tests and procedures done during the study that are not listed above, that could be used for healthcare purposes, and that are performed by or read at any Emory Healthcare facility, will be included in any Emory Healthcare medical record that your child has. Persons who have access to your child's medical record will be able to have access to all results that are placed there, and the results may be used by Emory Healthcare facilities to help provide your child with medical care. Any results that are kept as part of your medical record are not covered by certain state and federal laws and regulations that may prevent the disclosure of research data. However, the confidentiality of the results in the medical record will be governed by laws such as HIPAA that concern medical records.

Emory University does not have any control over results from tests and procedures performed and/or analyzed or read at non-Emory Healthcare facilities. These results are NOT routinely included in medical records at Emory Healthcare facilities, and they will not necessarily be available to Emory Healthcare providers. Emory University also does not have control over any other medical records that your child may have with other healthcare providers and will not send any test or procedure results from the study to these providers. It is up to you to let these healthcare providers know that your child is participating in a clinical trial.

Some tests and procedures that may be performed during this study by Emory Healthcare or other facilities or persons MAY NOT BE LOOKED AT OR READ FOR

ANY HEALTHCARE TREATMENT OR DIAGNOSTIC PURPOSES. THESE TESTS AND PROCEDURES WILL ONLY BE LOOKED AT FOR RESEARCH PURPOSES AND THE RESULTS WILL NOT BE REVIEWED TO MAKE DECISIONS ABOUT YOUR PERSONAL HEALTH OR TREATMENT. The specific types of tests or procedures, if any, that fall within this category are listed below: buccal smears for apoE genotype determination.

Due to confidentiality considerations, the Emory IRB has determined that a copy of your signed Informed Consent form and signed HIPAA Authorization form should not be included in your medical record. Accordingly, if you have an Emory Healthcare medical record, copies of these forms will not be placed there.

We encourage you to let your health care provider know that your child is participating in the study so that they can have all relevant information that they need when they make decisions about your child's health care.

This study is covered by a Certificate of Confidentiality that is granted by the National Institutes of Health. A Certificate of Confidentiality is used to try to protect identifiable, Sensitive Information about your child from the research from being released by the researcher in response to a subpoena or other legal request for information. Sensitive Information is identifiable information that may cause your child harm or cause damage to your child's reputation, financial standing, employability or insurability.

Even though there is a Certificate of Confidentiality for this study, the researcher will make the following voluntary disclosures of identifiable information about your child from the study: disclosure of subject information to the study sponsor; inclusion of any information in medical record; inclusion of subject name, fact of participation in a study, and contact information for principal investigator in the Clinical Trials Database maintained by the Clinical Trials Office for patient safety and account administration purposes; disclosure of information to state public health authorities to whom certain diseases are reported; disclosure to law enforcement authorities of any information that may indicate that child abuse has occurred; disclosure to appropriate individuals of information that is necessary to prevent immediate and substantial harm to subject or to others, etc. Any of this information that is disclosed will not be protected by the Certificate of Confidentiality.

In addition, any study test or procedure results or other study information or documents, if any, that are included in your medical record will not be covered by the Certificate of Confidentiality and may be released if requested by a lawful subpoena or other lawful and appropriate request for the information. Persons who have access to your medical record will have access to any study related information or documents that are in the record. Documents in your medical record will not be covered by certain state and federal laws and regulations that concern and may prevent the disclosure of research data, but confidentiality of any information in your medical record, however, is covered by laws such as HIPAA.

Costs & Compensation:

There will be no cost to you or your child for being in this study.

Your child will not receive additional compensation for this part of the study visit.

We will arrange for emergency care if your child is injured by this research. However, Emory University has not set aside funds to pay for this care or to compensate you if a mishap occurs. If you believe you have been injured by this research, you should contact Dr. Barbara J. Stoll, the investigator in charge at 404-778-1450.

Voluntary Participation/Withdrawal:

Participation in the study is voluntary. You have the right to refuse to let your child be in this study. If you decide to let your child be in this study and change your mind, you have the right to drop out at any time. This decision will not affect in any way your child's current or future medical care. This decision will not affect any other benefits to which you are otherwise given.

Contact Persons:

If you have any questions about this study call Ellen Hale, RN, research nurse coordinator. Call Dr. Barbara Stoll if you have been harmed from being in this study. Call Dr. Colleen Dilorio, chair of the Emory University Institutional Review Board if you have any questions about your rights as a participant in this research study. If you are a patient receiving care from the Grady Health System, and you have a question about your rights, you may contact Dr. Curtis Lewis, Senior Vice President for Medical Affairs at (404) 616-4261.

Their telephone numbers are:
Colleen Dilorio, M.D.: (404) 712-0720 or toll free at 1-877-503-9797
Barbara Stoll, M.D.: (404) 778-1450 Ellen Hale, R.N.: (404) 616-4218

We will give you a copy of this consent form to keep.
Your signature below indicates that you agree to volunteer your child for this study.

_____
Subject's Name

Signature of Subject's Legally Authorized Representative	*Date*	*Time*
Signature of Person Obtaining Consent	*Date*	*Time*

IRB#: 322-99
Consent Form Approval Period
FROM: 4/10/08 **TO:** 3/10/09
AUTHORIZATION: DC

Emory University School of Medicine

Research Subject HIPAA **Authorization** to Use or Disclose Health Information that Identifies You for a Research Study

Name of Study: "Association of Apolipoprotein E (apoE) genotype with brain injury and neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy" A Secondary Study for Extended Follow-up of the Hypothermia Trial Study

Study Number:_____

Name of Principal Investigator: Barbara J. Stoll, M.D.

Ira Adams-Chapman, M.D., Co-PI

Subject Name:_____

The privacy of your child's health information is important to us. In protecting your child's health information that identifies them, we will follow all requirements of the Health Insurance Portability and Accountability Act ("HIPAA" for short) that apply. This form will let you know how we will use any health information that you give us for this study that identifies your child. :

Please read this form carefully and if you agree with it, sign it at the end.

Research Study: The purpose of this study is to try to understand the presence of certain genes (genetic material) in your child.

People That Will Use or Disclose Your Health Information that Identifies You and Purpose of Use/Disclosure:

The following people and groups will use and disclose your health information in connection with the study. In this form, all of these people and groups are called the "Information Users":

The principal investigator, his/her research staff and people and organizations that he uses to help him conduct the Research Study will use and disclose your health information to do this work.

The NICHD is/are the sponsor(s) of this Research. The sponsor(s) and all other people and organizations that the sponsor(s) retain(s) to help it conduct and oversee the Research Study may use and disclose your health information to make sure that the research is being done correctly and to collect and analyze the results of the research.

There are a number of University persons/units, government agencies and other individuals and organizations that may use and disclose your health

information to make sure that the Research Study is being conducted correctly and safely, and to monitor and regulate the research or public health issues. These people and organizations include the following: the Emory University Institutional Review Board; Grady Research Oversight Committee (ROC); Children's Healthcare of Atlanta IRB; the Emory University Clinical Trials Office; Dr. Ricki Goldstein's lab at Duke University; the Emory University Office of Research Compliance; Research Triangle Institute (RTI); research monitors and reviewers; data safety monitoring boards; any government agencies who regulate the research including the Office of Human Subjects Research Protections

By signing this document you agree to allow any of these Information Users to use or disclose your child's health information that identifies them in order to conduct the Research Study, or to monitor or regulate research. In addition, we will comply with any laws that require us to disclose your child's health information, such as laws that require us to report child abuse or elder abuse. We also will comply with legal requests, or orders that that require us to disclose your child's health information, such as subpoenas or court orders. Finally, we may share your health information with a public health authority that the law authorizes to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and/or conducting public health surveillance, investigations or interventions.

Description of Health Information that Identifies Your Child that Will be Used or Disclosed

The Information Users may use or disclose the following health information about your child: study results

Revoking your Authorization:
You do not have to sign this Authorization. In addition, if you sign this Authorization, later, you may change your mind at any time and revoke (take back) this Authorization. If you want to revoke this Authorization you must write to: Barbara J. Stoll, M.D., PO Box 26018, 29 Jesse Hill, Jr. Drive, Atlanta, GA 30303.

If you revoke your Authorization, the Researchers will not collect any more health information that identifies your child, but they may use or disclose identifiable information that you already gave them in order to notify any of the other Information Users that you have taken back your authorization; to maintain the integrity or reliability of the Research Study; and to comply with any law that they are required to obey.

Other Items You Should Know:

HIPAA only applies to people or organizations that are health care providers, health care payers or healthcare clearinghouses. HIPAA may not apply to all Information Users. If HIPAA doesn't apply to an Information User, then that User doesn't have to follow HIPAA requirements when it uses or discloses your health information..

You do not have to sign this authorization form, but if you do not, you may not participate in the Research Study or receive research-related treatment. You may still receive non-research related treatment.

If the Research Study involves medical treatment, then, in order to maintain the integrity of the research study, you generally will not have access to your child's personal health information related to this Research Study until the study is complete. When the study is complete, then, at your request, you may generally have access to any of your child's personal health information related to the research that makes up a part of the medical information and/or other records that your child's health care providers use to make decisions about your child. If access to this information is needed before the end of the Research Study for your child's treatment, then the information may be provided to your child's physician.

If your identifying information is removed from your child's health information, then the information that remains will not be subject to this authorization or covered by HIPAA, and it may be used or disclosed to other persons or organizations, and/or for other purposes.

Expiration Date: This authorization will expire when the research study and all study related activities are complete.

As a study participant, if you any questions regarding the study, you may call Dr. Barbara Stoll the study's Principal Investigator at (404) 788-1450. If you have any questions regarding your rights as a study subject, you may call Dr. Colleen DiIorio, Chair of the Emory University Institutional Review Board at (404) 712-0720.

A copy of this authorization form will be given to you.

_____

Signature of Study Subject OR Subject's Legal Authorized Representative

Date _____ Time_____

_____

Printed Name of Study Subject OR Subject's Legally Authorized Representative

If Representative, Relationship to Study Subject: _____

_____

Signature of Person Obtaining Authorization

_____ _____

Date Time

IRB#: 322-99

Consent Form Approval Period

FROM: 4/10/08 TO: 3/10/09

AUTHORIZATION: AC

Version Date(s): 4/01/2008

Emory University School of Medicine
Department of Pediatrics

Title: "Association of Apolipoprotein E (apoE) genotype with brain injury and neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy" A Secondary Study for Extended Follow-up of the Hypothermia Trial Study

Principal Investigator: Barbara J. Stoll, M.D.
Ira Adams-Chapman, M.D., Co-PI

Sponsor: National Institute of Child Health and Human Development

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What is this study about?
★ We want to look at special cells in your mouth.

How does this study work?
★ Your parent (or the person taking care of you) has given permission for you to be in this study. If both of you agree, we will gently rub a Q-tip inside your cheek. This will not take very long to do. It will feel like a tickle in your mouth.

Can you say "NO"?
★ You do not have to be in this study if you do not want to be. Your doctor will still take care of you in the same way whether you are in the study or not, or if you decide to quit later.

Will this study hurt?
★ It will not hurt to be in this study?

How may this study help you?
★ You may not be helped by this study. We may learn things about you to help other children.

We will ask you if you want to be in this study.

_____
Participant Name

□ Verbal informed assent has been obtained.

□ In my opinion this child cannot give informed assent.
Reason(s):_____

_____

_____ _____ _____
Person obtaining assent Date Time

4/01/2008

IRB#: 322-99
Consent Form Approval Period
FROM: 4/16/08 TO: 3/10/09
AUTHORIZATION: DC

Barbara J. Stoll, M.D.

PO Box 26015

80 Jesse Hill, Jr. Dr.

Atlanta, GA 30303

"Association of Apolipoprotein E (apoE) genotype with brain injury and neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy"
A Secondary Study for Extended Follow-up of the Hypothermia Trial Study

Dear Dr. Stoll:

I want to end my participation in the research study that is named above. In addition to ending my participation I would like to [choose one of the following options]:

REVOKE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not participate in the research study, and I revoke my authorization to permit the researchers to collect and use any more information about me. I understand and agree that in certain circumstances the researchers may need to use my information even though I have revoked my authorization, for example, to let me know about any safety concerns, or to make any required reports to governmental regulatory agencies.

CONTINUE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not actively participate in the research study any more, but the researchers may continue to collect and use information from my medical record as needed for the research study, but only for the reasons discussed in the consent form that I signed.

I understand that the researchers will respond to this letter by letting me know that they have received it.

Sincerely,

IRB#: 322-99

Consent Form Approval Period
FROM: 4/16/08 **TO:** 3/10/09
AUTHORIZATION: SC

4/1/2008

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Susie Buchter
Subject: SAE for SUPPORT
Date: Thursday, April 17, 2008 3:20:41 PM

Dear Rose,
We will be sending you the SAE report tomorrow for a new baby that was enrolled into SUPPORT during the night. This is Network (b) (6) This mom had premature rupture of membranes. Mom delivered at 24 6/7 weeks. She was found (b) (6) The baby was depressed at birth and had some chest compressions with PPV and improved around 3 minutes. Baby was randomized to CPAP and after resuscitation, was placed on CPAP. Condition improved after admission to NICU. SAE not related to study.

Will send complete report with Medwatch tomorrow.

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: Missing SUPPORT outcomes
Date: Thursday, April 17, 2008 2:33:15 PM
Attachments: Infants with missing outcomes 04-16-08.xls

Rose,

Attached is the list of infants with missing SUPPORT outcomes this month. Note that the ROP list includes error messages for 7 infants who actually *do* have ROP status, but whose SUPP10 has inconsistencies that need to be cleared up.

Thanks,
Marie

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

Missing_BPD

CENTER	NETWORK	BPD_message
3	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
13		Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
19		Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing
19		Infant was eligible for challenge (per PHY01) but outcome was not entered on PHY02RA
19		Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT FU
Date: Thursday, April 17, 2008 12:30:40 PM
Attachments: FU pending at former centers 04-16-08.xls

Of the SUPPORT infants at Miami, Rochester and Wake Forest, all have had follow-up except three that were lost to FU and one (center 21, network (b) (6) whose window closed on 4/14/2008 (see attached).

Marie

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

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 08, 2008 1:55 AM
To: Das, Abhik; Gantz, Marie
Subject: SUPPORT FU

Can you tell me how many and the study numbers of children with FU pending for SUPPORT from Miami, Rochester, Wake Forest?
Also, though with missing forms from those sites?
It can wait a few weeks.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

Missing_FU

FCENTER	FOLNUM	CENTER	NETWORK	FU window start	FU window end	FU status (NF10)
	(b) (6)	21	(b) (6)	11/30/07	04/14/08	
8		8		02/23/07	07/08/07	4=Lost to FU
8		8		07/18/07	12/03/07	4=Lost to FU
21		21		06/22/07	11/06/07	4=Lost to FU

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Late surfactant administration for SUPPORT infants
Date: Friday, April 11, 2008 3:46:01 PM

Thanks

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 11, 2008 12:45 PM
To: Finer, Neil
Cc: Rich, Wade; Martinez, Fernando
Subject: RE: Late surfactant administration for SUPPORT infants

1-866-675(b) (6)with passcode (b) (6)

Thanks
Roes

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, April 11, 2008 3:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; Martinez, Fernando
Subject: RE: Late surfactant administration for SUPPORT infants

Rose
Will you or Carolyn please send me the call in number of our meeting for Monday?
Thanks
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 10, 2008 11:43 AM
To: Finer, Neil
Subject: RE: Late surfactant administration for SUPPORT infants

You can discuss

Thanks
Rose

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, April 10, 2008 2:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Late surfactant administration for SUPPORT infants

Hi Rose
I would recirculate the materials from the phone call with this new information on Surfactant. The agenda should really be to discuss any concerns from our previous discussion and to hear reports from the Secondaries.
Do you want me to do this or will you?
Thanks
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 10, 2008 7:20 AM
To: Finer, Neil
Subject: FW: Late surfactant administration for SUPPORT infants

Neil
Do you want copies of this (or the other materials from the call) for the SC meeting next week?
Let me know
Rose

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, April 02, 2008 5:42 PM
To: Finer, Neil
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Late surfactant administration for SUPPORT infants

Neil,

In response to questions yesterday in the SUPPORT subcommittee meeting, here is some additional information on protocol deviations pertaining to late surfactant administration.

The 37 protocol deviations reported in the SUPPORT update (9 cases before January 1, 2006, and 28 cases after) include all protocol deviations for late surfactant entered on SUPP06, and additional deviations for the surfactant treatment group that were not reported on SUPP06 but were found using

forms SUPP03 and SUPP04. Protocol deviations reported on the SUPP06 were for 29 infants assigned to surfactant and 8 infants assigned to CPAP. There were 4 cases reported on SUPP06 in which surfactant was not given at all; those babies were assigned to CPAP. In the remaining cases, surfactant was given at 1.2 – 3.4 hours post-birth, with a median time of 1.6 hours. Reasons for the deviations (when provided on SUPP06) are listed in the attached document.

In addition to the 37 deviations included in the SUPPORT update, there are 26 additional cases in which infants assigned to CPAP were intubated in the DR but received surfactant after 1 hour of life. In those cases, surfactant was given at 1.2 – 3.2 hours, with a median of 1.8 hours. The number of cases by center is attached. Please let me know if you would like RTI to ask the centers to enter protocol deviations for the cases. I apologize for not including these deviations in the SUPPORT update; when I originally looked at late surfactant use on the SUPP03 and SUPP04 I was focusing only on the infants assigned to surfactant.

Let me know if you have any questions or would like additional information.

Marie

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

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT secondary update
Date: Friday, April 11, 2008 3:41:28 PM
Attachments: April2008SUPPORTNeuroUpdateHINTZ.doc

Hi Rose

I am bringing copies of these to the Steering Committee meeting.
Just wanted you to have electronic copies. I sent also to Neil.

Thanks

susan

1) Enrollment/Process update

- 15 sites now enrolling
- From monthly report and additional routine data query from RTI (through 3/31/2008)
    - **414 patients** have been enrolled in the SUPPORT Neuroimaging secondary
        - **~304 patients** have complete 35-42 week imaging *including MRI*
            - **Of the 110 patients enrolled without MRI:**
                - 59 patients died before MRI
                - 33 with MRI01 not yet complete or window not reached
                - 18 with other issues
                    - Includes clinically unstable (2), movement or uncooperative (3), transferred/discharged (2), technical issues (6), miscellaneous (5)
- MRI central reading –
    - Rolling central reading for SUPPORT MRI's is on hold while Hypothermia MRI's are in process
- THANK YOU to all sites for their diligence in sending MRI's and CUS on a routine basis to RTI

2) Tracking enrollment

- THANK YOU to all the coordinators who are keying the FIRST PART of the MRI01 form as soon as they can.

3) PROPOSED Extended Follow-up at 6-7 years for SUPPORT Neuroimaging cohort

- Proposal reviewed by the Protocol Review Subcommittee
    - Recommended for presentation to the Steering Committee (April meeting)
    - PI's will discuss with their sites, then a vote on feasibility/scientific merit will occur (Vote #1). If that is favorable, a priority vote will occur (Vote #2).

4) Please call or email with questions, comments, and suggestions

Susan Hintz
650-723-5711 (office)
Email: srhintz@stanford.edu

THANKS TO ALL THE SITES FOR THEIR HARD WORK ON THIS STUDY!

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject: FW: SUPPORT updates
Date: Thursday, April 10, 2008 2:59:19 PM
Attachments: SUPPORT Enrollment 3-27-08.doc
SUPPORT Adverse Events 03-27-08.doc
SUPPORT Use of HFNC 03-27-08.doc
SUPPORT Protocol Deviations - old vs new 03-27-08.doc
SUPPORT Protocol Deviations by center - old vs new 03-27-08.doc
All Centers pct in range through Mar08.rtf
Breathing Outcomes Update-April 08.doc
Working Memory in ELBW 12-1-07 (2).doc
Proposal for ancillary study to Support Trial Working Memory(2).doc
Late surf reasons from SUPP06 3-27-08.doc
Late surf for CPAP by center 3-27-08.rtf

Hello Everyone
For the Steering Committee we will review any issues from this previous phone agenda.
In addition we will hear reports form the Secondaries.
If you have any other items please forward them to me or Rose.
As of today we are at or greater than 1000 infants. Great work everyone!!!
I have added the actual Surfactant protocol deviations for your review.
Talk to you next week
Safe travels
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Finer, Neil
Sent: Friday, March 28, 2008 10:45 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade
Subject: FW: SUPPORT updates

Hi Everyone
Here is an agenda for next weeks phone meeting, and the updates from Marie. Thanks Marie for getting this data to us.

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations (Currently 990 per August > 75% of total, completion will take another 9-11 months for enrollment)
The adverse events are lower than baseline in all categories but the NRN baseline may have also moved lower. The only area not lower, but not higher by any significant amount is the air leak information
The commonest protocol deviation is failure to use the study oximeter and next is the timing of surfactant.
Marie has removed the HFNC use and separately indicated its use

2. Discuss any oximeter issues – concerns regarding Sat Share from UK trial, and New Mexico oximeters, and any data loss from Masimo software/hardware

3. Review status of Secondaries-
   MRI S Hintz to report – Discuss Longer Term follow-up
   Breathing Outcomes - See Tim's report - Attached
   Nutrition
   Antenatal consent

4. Discuss Ancillary – New Mexico Working Memory and MRI (Attached) – My main concern is that this study is not linked to the hypotheses in SUPPORT. My understanding is that any Ancillary/Secondary should have such a link as the population will be potentially affected in any outcome measure by the randomized interventions.

5. Data Sharing with NeoProm – The prospective Meta Analysis – ie Enrollements, consents, oximeter compliance.
6. Other Issues

Please let me know if there are additional issues you would like added to the agenda

Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
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SUPPORT Enrollment as of March 27, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	990	76%

Enrollment by Center

Center	<Oct-07	Oct-07	Nov-07	Dec-07	Jan-08	Feb-08	Mar-08	Total
3	71	4	3	1	2	3	4	88
4	44	1	1	0	0	1	5	52
5	30	3	3	3	4	1	2	46
8	17	0	0	0	0	0	0	17
9	57	2	0	0	1	0	2	62
11	62	1	2	0	5	0	0	70
12	48	1	2	2	2	2	1	58
13	20	0	1	0	4	0	0	25
14	78	0	1	3	6	2	5	95
15	30	0	3	1	0	1	2	37
16	108	4	6	6	9	2	8	143
18	58	0	2	2	0	1	1	64
19	41	4	1	3	2	0	0	51
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	52	1	3	0	0	1	0	57
23	37	1	1	1	0	1	1	42
24	11	1	4	1	1	2	0	20
25	26	1	2	0	0	1	4	34
26	8	2	0	0	1	0	1	12
Total	815	26	35	23	37	18	36	990
Centers		17	17	17	17	17	17	
Avg/center		1.5	2.1	1.4	2.2	1.1	2.1	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	9
2.5	8
3	6

Percent of SUPPORT infants with selected adverse events as of March 27, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.3	9.2	4.1
Air leak	8.5	11.1	6.6
Pulmonary hemorrhage	6.4	10.0	3.8
Severe IVH (grades III-IV)	14.0	19.0	10.4

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of March 27, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			3	5%
4			8	19%
5			7	15%
9			12	24%
11	1	5%	6	12%
12			9	19%
13			4	17%
14	1	5%	6	8%
15			1	3%
16			3	3%
18	1	5%	7	16%
19			9	25%
22			1	6%
23			1	2%
24			1	5%
25			7	21%
Total	3	1%	85	11%

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	3
Surfactant not given in the first hour	28
Oximeter not started within 2 hours	17
Infant placed on study oximeter for incorrect treatment	10
Failure to use study oximeter at times required by protocol	57
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	8
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	20
Other	4
Total	185

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	48
Infant placed on study oximeter for incorrect treatment	10
Failure to use study oximeter at times required by protocol	57
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	8
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	20
Other	4
Total	185

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	1
Surfactant not given in the first hour	9
Oximeter not started within 2 hours	7
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	58

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	17
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	58

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			1								1	1									3
Surfactant not given in the first hour	3	4				4	1	2	2		4		1					4	3		28
Oximeter not started within 2 hours	1	2	1			1	2			2	1	1	1			1	2	1	1		17
Infant placed on study oximeter for incorrect treatment	2		1			1	1				2		1				1		1		10
Failure to use study oximeter at times required by protocol	1	4	9		2	4	5	1	8		6		2				3	4	5	3	57
Non-study (unmasked) oximeter used at same time as study ox.						2	1			1			1						2		7
Mechanical ventilation initiated for other than study criteria																	1				1
NSIMV initiated in infant not previously intubated	1				1						4										6
Extubation (excluding unplanned) for other than study criteria						3			4		1										8
Failure to extubate CPAP infant if all criteria met								1		2											3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1										2
Infant received postnatal steroids in first 21 days of life	1					2		1	4		2	6	1				1				18
Randomization/consent errors	1	1	2		3	1				2		3	2			1	4				20
Other									1	1	1								1		4
Total	10	11	15	0	6	19	10	5	19	8	23	11	9	0	0	2	12	9	13	3	185

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2%								1%	2%									0%
Surfactant not given in the first hour	5%	10%				8%	2%	8%	3%		4%		3%					20%	9%		4%
Oximeter not started within 2 hours	2%	5%	2%			2%	4%			6%	1%	2%	3%			6%	5%	5%	3%		2%
Infant placed on study oximeter for incorrect treatment	3%		2%			2%	2%				2%		3%				2%		3%		2%
Failure to use study oximeter at times required by protocol	2%	10%	20%		4%	8%	10%	4%	11%		6%		6%				7%	20%	15%	25%	7%
Non-study (unmasked) oximeter used at same time as study ox.						4%	2%			3%			3%						6%		1%
Mechanical ventilation initiated for other than study criteria																	2%				0%
NSIMV initiated in infant not previously intubated	2%				2%						4%										1%
Extubation (excluding unplanned) for other than study criteria						6%			5%		1%										1%
Failure to extubate CPAP infant if all criteria met								4%		6%											1%
Failure to extubate surfactant infant if all criteria met						2%															0%
Infant intubated without meeting study criteria			2%								1%										0%
Infant received postnatal steroids in first 21 days of life	2%					4%		4%	5%		2%	13%	3%				2%				2%
Randomization/consent errors	2%	2%	4%		6%	2%				6%		7%	6%			6%	10%				2%
Other									1%	3%	1%								3%		1%
Total protocol deviations	16%	26%	33%		12%	37%	21%	21%	26%	23%	22%	24%	25%		0%	13%	29%	45%	38%	25%	25%
Total number of infants enrolled	64	42	46	0	49	51	48	24	73	35	105	45	36	0	1	16	42	20	34	12	743

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											1										1
Surfactant not given in the first hour	4			1		2	1				1										9
Oximeter not started within 2 hours						1					5	1									7
Infant placed on study oximeter for incorrect treatment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox.															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1											1	2							4
Other																					2
Total	7	4	0	2	0	7	1	0	4	0	17	2	1	3	3	7	0	0	0	0	58

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											3%										0%
Surfactant not given in the first hour	17%			6%		11%	10%				3%										4%
Oximeter not started within 2 hours						5%					13%	5%									2%
Infant placed on study oximeter for incorrect treatment	4%			6%							11%					2%					2%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						7%
Non-study (unmasked) oximeter used at same time as study ox.															14%						1%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	29%	40%		12%	0%	37%	10%	0%	18%	0%	45%	11%	7%	33%	43%	17%					24%
Total number of infants enrolled*	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-95	Percent
Jan08-Mar08	Days of life 1-14	All centers	2338	38.5	7.9	76.6	15.5
		Center 16	767	37.7	8.6	80.6	10.8
	Day 15 to 36 wks	All centers	2960	33.2	12.7	71.5	15.8
		Center 16	1887	34.8	13.3	71.3	15.4
Oct07-Dec07	Days of life 1-14	All centers	11954	30.9	9.3	77.8	12.9
		Center 3	1379	34.7	8.7	77.7	13.6
		Center 5	2166	28.3	8.4	69.8	21.8
		Center 14	561	35.5	6.9	80.4	12.6
		Center 15	502	25.7	14.6	75.2	10.2
		Center 16	2717	39.7	10.5	84.4	5.2
		Center 18	1111	31.7	8.6	79.7	11.7
	Day 15 to 36 wks	All centers	45917	24.9	13.1	65.9	21.0
		Center 3	4704	30.8	14.9	69.1	15.9
		Center 5	8865	22.3	10.8	61.3	27.9
		Center 11	1141	24.6	10.2	54.2	35.6
		Center 12	1573	28.6	7.1	63.9	29.0
		Center 14	1386	20.9	13.3	63.9	22.8
		Center 15	3221	22.6	18.6	64.4	17.0
		Center 16	7385	26.1	14.8	70.6	14.5
		Center 18	1747	26.5	16.3	73.1	10.6
		Center 23	2680	28.8	10.8	61.4	27.8
		Center 25	6601	23.8	9.8	73.1	17.1
Jul07-Sep07	Days of life 1-14	All centers	14403	33.6	7.5	75.7	16.8
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1394	34.8	9.6	74.8	15.6
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 16	1162	39.8	7.4	81.8	10.7
		Center 23	2150	32.6	5.5	71.6	23.0
		Center 25	1723	39.7	5.9	83.1	11.0
	Day 15 to 36 wks	All centers	53770	24.9	11.5	65.3	23.2
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5330	22.2	9.9	59.6	30.5
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	14969	34.4	9.1	76.7	14.2
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1061	31.1	11.6	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1439	40.3	8.5	85.7	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	685	16.3	7.9	69.3	22.8
	Day 15 to 36 wks	All centers	55282	28.6	12.1	65.8	22.0
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		Center 11	4086	23.7	10.1	57.7	32.2
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	4710	29.9	13.1	69.8	17.1
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2858	22.4	9.4	55.4	35.2
Jan07-Mar07	Days of life 1-14	All centers	16812	35.4	8.3	78.1	13.6
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	54926	27.9	12.5	68.9	18.6
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 16	3353	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	4307	20.2	17.7	64.5	17.8
Mar06-Dec06	Days of life 1-14	All centers	32802	37.2	8.2	79.0	12.9
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2419	33.1	9.1	67.5	23.4
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5667	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	881	30.5	6.0	77.5	16.6
		Center 25	1138	48.0	6.4	83.5	10.1
	Day 15 to 36 wks	All centers	107046	29.2	12.6	68.4	19.0
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3278	29.7	11.8	72.9	15.3
		[illegible]	5915	29.9	10.4	61.4	28.2
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14390	29.2	12.5	69.1	18.5
		Center 18	15423	23.7	17.0	66.0	17.0
		Center 19	1281	26.6	8.0	59.8	32.3
		Center 25	6484	39.9	9.3	77.0	13.7

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Through Feb06	Days of life 1-14	All centers	27159	38.0	9.4	79.6	11.1
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1448	32.0	10.0	77.5	12.5
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1517	42.1	9.5	85.5	5.0
		Center 22	3531	40.0	8.7	79.9	11.3
	Day 15 to 36 wks	All centers	133388	26.5	12.2	67.6	20.2
		Center 3	13570	17.7	17.4	64.2	18.4
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	4802	17.3	8.5	58.1	33.4
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	8688	28.1	17.8	63.6	18.6
		Center 19	1919	32.8	7.0	73.3	19.8
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	3563	29.6	16.7	68.7	14.6
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

Breathing Outcomes Update

3/27/08

Tim Stevens

Enrollment

Enrollment into The Breathing Outcomes Study is progressing well. In the period December 31st to February 29th, 53 patients became eligible for follow up (i.e. survived to discharge or status) and 31 patients were consented into Breathing Outcomes. As can be seen in the far right column below, the difference between the number of patients eligible for follow up and the number for whom consent has been obtained has varied by quarter but has remained relatively consistent in the 130-150s, suggesting that participation in Breathing Outcomes is increasing in lock step with the number of SUPPORT patients surviving to discharge or status. The variation is likely related to a delay in data entry during the prior period. The baseline difference (139 patients) reflects the delay between onset of SUPPORT and the beginning of Breathing Outcomes.

Follow-up

Interval data on the questionnaire follow up rate at each of the 4 time points is presented on the next page (*Table 1b - Data as of 3/19/08)*. Follow-up rates at each time point exceed 90%. Over 72% of enrolled patients who have passed the 18-22 month window have completed each of the 4 questionnaires.

Individual center follow-up rates are strong at all centers with the possible exception of Indiana where follow up rates are 63% and 46% at the 6 and 12 month time points, respectively, and among 9 infants who have passed through the 18-22 month time point, none have successfully completed all 4 questionnaires.

Other Issues

- The NRN Steering Committee has granted approval to Drs. Jon Davis and Richard Parad (recombinant SOD Trial) and Dr. Roberta Ballard (Trial of Late SURFactant – TOLSURF Study) to use of the Breathing Outcomes questionnaires and manual of procedures to assess outpatient pulmonary outcomes as part of their randomized controlled trials.

- Richard Ehrenkranz, Neil Finer and I have discussed a potential concept proposal to continue pulmonary follow up of SUPPORT and Breathing Outcomes Study patients through school age. Outcome measures would include spirometry and symptom questionnaires with analysis by SUPPORT intervention assignment.

Breathing Outcomes Enrollment
December 31, 2007 - February 29, 2008

Enrollment

Breathing Outcomes
From SUPPORT start date to:

	Follow up Expected	Consent	Discharge Form	6 month	12 month	18 month	Follow up expected minus consent
30-Nov-06	327	188	186	120	75	0	139
31-Mar-07	416	279	276	161	121	29	137
30-Sep-07	613	456	402	277	173	121	157
31-Dec-07	663	529	520	357	236	139	134
29-Feb-08	716	560	548	404	277	154	156
Difference 31-Dec-07 to 29-Feb-08	53	31	28	47	41	15	

NICHD Neonatal Research Network

Breathing Outcomes Protocol

Table 1b - Data as of 3/19/08
Number and Percent of Questionnaires Completed at Each Point in Time
By Center

Center Name	SUPF00 Consent Granted[1]	SUPF01 Baseline Complete[2]		SUPF02 6 Month Complete[3]		SUPF02 12 Month Complete[4]		SUPF03 18-22 Month Complete[5]		Complete Series & Entered 18 Month Window[6]
	Number	Number	%	Number	%	Number	%	Number	%	% (count)
Case Western Univ	56	56	100.00%	41	93.18%	33	97.06%	19	90.48%	70.37% (19/27)
Univ. of Texas (D)	35	35	100.00%	30	100.00%	20	100.00%	9	100.00%	81.82% (9/11)
Wayne State Univ	22	19	86.36%	9	90.00%	5	83.33%			0.00% (0/4)
Univ. of Miami	11	11	100.00%	11	100.00%	10	90.91%	10	90.91%	81.82% (9/11)
Emory University	29	29	100.00%	25	100.00%	19	95.00%	10	100.00%	83.33% (10/12)
Univ. of Cincinnati	49	49	100.00%	27	72.97%	25	96.15%	12	92.31%	30.77% (4/13)
Indiana Univ.	32	24	75.00%	14	63.64%	6	46.15%	8	100.00%	0.00% (0/9)
Yale University	18	18	100.00%	16	100.00%	4	100.00%	1	100.00%	50.00% (1/2)
Brown University	68	65	95.59%	43	79.63%	31	88.57%	13	81.25%	55.00% (11/20)
Stanford University	13	10	76.92%	7	100.00%	1	100.00%	1	100.00%	100.00%(1/1)
Univ. of Alabama	81	74	91.36%	61	100.00%	40	100.00%	15	100.00%	100.00%(15/15)
Univ. of Texas (H)	32	32	100.00%	27	100.00%	21	95.45%	8	100.00%	88.89% (8/9)
Duke University	8	8	100.00%	8	100.00%	8	100.00%	7	100.00%	100.00%(7/7)
Wake Forest	9	9	100.00%	9	100.00%	9	100.00%	9	100.00%	100.00%(9/9)
Children's (NY)	5	5	100.00%	5	100.00%	5	100.00%	4	100.00%	80.00% (4/5)
Univ. of Calif. At San Diego	31	31	100.00%	29	100.00%	24	96.00%	24	96.00%	96.00% (24/25)
Tufts NEMC	30	30	100.00%	15	100.00%	1	50.00%			
University of Iowa	12	12	100.00%	7	77.78%					
University of Utah	20	18	90.00%	8	100.00%	8	100.00%			
University of NM	6	6	100.00%	5	100.00%					
TOTAL	567	541	95.41%	397	91.90%	270	93.43%	150	94.94%	72.78% (131/180)

Footnotes

NICHD Neonatal Research Network

Breathing Outcomes Protocol

Table 1b - Data as of 3/19/08
Number and Percent of Questionnaires Completed at Each Point in Time
By Center

[1] Column 1 "SUPF00 Consent Granted" - A simple count of the number of infants in each Center for which consent has been granted.

[2] Columns 2 and 3 "SUPF01 Baseline Complete" - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF01 "Was the interview conducted," and have a Baseline interview status of "Complete." The denominator for the "%" column includes infants for which consent has been granted.

[3] Columns 4 and 5 "SUPF02 6 Month Complete" - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 "Was the interview conducted," and have a 6 Month interview status of "Complete." The denominator for the "%" column includes infants for which consent has been granted and have a 6 Month interview status of "Complete" or "Out of Window."

[4] Columns 6 and 7 "SUPF02 12 Month Complete" - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 "Was the interview conducted," and have a 12 Month interview status of "Complete." The denominator for the "%" column includes infants for which consent has been granted and have a 12 Month interview status of "Complete" or "Out of Window."

[5] Columns 8 and 9 "SUPF03 18-22 Month Complete" - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF03 "Was the interview conducted," and have a 18-22 Month interview status of "Complete." The denominator for the "%" column includes infants for which consent has been granted and have a 18-22 Month interview status of "Complete" or "Out of Window."

[6] Column 10 "Complete Series & Entered 18 Month Window" – The numerator is the number of infants in each Center for which consent has been granted, have an answer to the questions on forms SUPF01, SUPF02 (6 Month), SUPF02 (12 Month), and SUPF03 "Was the interview conducted," and have a interview status of "Complete" for all 4 stages (Baseline, 6 Month, 12 Month, and 18-22 Month). The denominator is the number of infants for which consent has been granted and who have an 18-22 interview status of "Complete," "Due," "Overdue," or "Out of Window" (i.e., all infants who have entered the window).

Running head: EARLY WORKING MEMORY IN INFANTS BORN ELBW

Early Working Memory and Cognition in a Cohort of Ethnically Diverse Infants Born Extremely Low Birth Weight

Jean Lowe, Peggy MacLean, Michele L. Shaffer, Kristi Watterberg

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INTRODUCTION:

Infants born extremely low birthweight (ELBW; <1000 grams) are at greater risk for early cognitive, attention and self-regulation difficulties (Vohr, Wright, Poole, & McDonald, 2005). These difficulties have also been shown to persist throughout childhood. Studies indicate, for instance, that children born ELBW have a higher incidence of learning difficulties, attention-deficit/ hyperactivity disorder, specific neuropsychological deficits, and behavioral problems throughout childhood (Anderson & Doyle, 2004; Hack, Friedman, & Fanaroff, 1996)

Recent research examining the role of early working memory difficulties in the cognitive, behavioral, and academic outcomes of children has highlighted the importance of working memory in outcomes of children born preterm (Woodward et al, 2005). Working memory refers to the process of holding task-relevant information in mind for brief intervals so that the information can be used to guide future actions (Goldman-Rakic, 1987) and is considered essential for higher order cognitive functioning (Bell & Wolfe, 2004). Studies examining early working memory have shown that children born preterm show impaired working memory throughout childhood (Rose and Feldman, 1996; Ross Boartright, Auld, & Nass, 1996; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Isaacs et al., 2000; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; Woodward, Edgin, Thompson, & Inder, 2005) and that impairment in this skill contributes significantly to later risks of global intellectual and academic difficulties at school in children born preterm (Rose, Feldman, & Wallace, 1992; Wolke & Meyer, 1999).

Further, there is increasing evidence that the ability to self-regulate affect and attention plays an essential role in working memory performance (Bell & Wolfe, 2004; Keenan, 2002). Previous studies have shown that infants who demonstrate self-regulatory problems have more difficulty exploring and attending to the environment, limiting their ability to engage effectively in working memory tasks (Bell & Wolfe, 2004; Keenan, 2002). Although the association between self-regulation and working memory performance has been demonstrated in infants born full-term (Bell & Wolfe, 2004; Keenan, 2002), no study to date has examined this relationship in a population of extremely preterm infants.

The purpose of this study was to better understand early working memory as measured by object permanence tasks in 18 – 22 month olds born ELBW, compared to measures of cognition and self-regulation (i.e., emotional and attentional regulation). We hypothesized that children with lower birthweights and higher illness severity would have more difficulty on the object permanence tasks. In addition we hypothesized that working memory problems would be directly related to difficulty in emotional and attention regulation. The impact of ethnicity, gender, illness severity, and family socio-economic status on object permanence performance was also examined. Object permanence performance was not expected to differ by ethnicity, given that these tasks should be culturally neutral.

METHODS

Population and study protocol

Infants eligible for this follow-up study were surviving infants who had been enrolled in a multicenter study of low-dose hydrocortisone therapy for prophylaxis of

early adrenal insufficiency. Singletons and twins between 500 and 999 grams birth weight were eligible if they were mechanically ventilated at study entry (12 - 48 hours postnatal age). The study protocol was approved by institutional review boards at all participating institutions and parental consent was obtained prior to enrollment. At the evaluation, demographic and medical histories were obtained. Weight, height and head circumference were recorded.

Development was assessed with the Bayley Scales of Infant Development II (BSID-II; 13) with a Mental Developmental Index (MDI) calculated as a measure of cognition. Emotional regulation and attentional regulation were assessed using the Emotional Regulation and Orientation/Engagement scales of the BSID-II Behavior Rating Scale, respectively. Items 84, 96, and 102 of the BSID-II Mental Scale were used as measures of object permanence. Children were asked to find a toy hidden under one of two cups with double visual displacement utilized (the toy was hidden under one cup, removed and hidden a second time under the second cup) to increase the difficulty of the item. The number of object permanence items correctly completed was calculated for each child. This number was dichotomized, grouping those who correctly completed 0 or 1 items **or those who correctly completed 2 or 3 items (which included the item with double visual displacement). Object permanence mastery was defined as correctly completing 2 or 3 items.** The Clinical Risk Index for Babies (CRIB) score, birthweight, and gestational age were used to examine medical illness severity, while household income and maternal education were used as family socio-economic variables. All examiners administering the BSID-II were trained and certified.

Statistical analysis

Neurodevelopmental outcomes were analyzed using analysis of covariance for continuous outcomes and logistic regression for binary outcomes. These analyses included adjustment for the stratification variable birth weight (continuous form) and the following baseline characteristics: gestational age, CRIB score, gender, ethnicity, maternal education and household income. Hydrocortisone treatment was not included as a variable in these analyses. For analysis of ethnic group, six children (4 Native American, 2 Black Hispanics) were omitted, as there were insufficient numbers to adequately study these groups and to avoid arbitrary pooling. Unless otherwise noted, all hypotheses tests were two-sided and used a significance level of 0.05. All statistical analyses were conducted using SAS Version 9 (SAS Institute Inc., Cary, NC). Family demographic characteristics at follow up are shown in Table 1 with children grouped by ethnicity/race.

RESULTS:

A significant relationship was found between object permanence and cognition (BSID-II MDI), such that, MDI scores increased as did the odds of object permanence mastery ($p<0.0001$). When adjusted for CRIB score, both MDI ($p<0.0001$) and CRIB ($p=0.04$) were significant. Object permanence mastery also had significant positive relationships with orientation/engagement (measure of attention) and emotional regulation scores (measure of self-regulation) on the Behavior Record of the Bayley Scales ($p<0.0001$ and $p=0.0004$ respectively). The relationship between object permanence mastery and Orientation/ Engagement as well as between object permanence mastery and Emotional Regulation remained significant after controlling for medical illness severity variables and socio-economic variables.

Girls performed significantly better than boys on object permanence tasks ($p=0.002$). When maternal education and household income were included as covariates, gender remained significant ($p=0.0004$). Neither socio-economic nor medical illness severity variables were significantly related to object permanence mastery.

No significant differences were found between ethnic groups in object permanence mastery; however, there was a significant effect of ethnic group on MDI score, such that Hispanic, Asians and African American infants had significantly lower MDI scores than Caucasian children (see Table 2). These differences remained significant after controlling for medical illness severity and socio-economic variables. A significant difference was also found on a measure of attentional regulation (BSID-II Orientation/Engagement), with Black children performing less well than Caucasian children (see Table 2).This difference could not be accounted for by socio-economic or medical illness severity variables. No ethnic differences were found on emotional regulation (BSID-II Emotional Regulation).

Ethnicity	MDI		Orientation Engagement	
	Mean ± SD	p-value*	Mean ± SD	p-value*
Caucasian (n=118)	85.90 ± 19.96		47.38 ± 28.09	
Black (n=90)	72.48 ± 15.95	<0.0001	38.29 ± 23.47	0.0156
Hispanic (n=25)	77.38 ± 16.52	0.04	45.24 ± 27.93	0.71
Asian (n=11)	69.27 ± 19.86	0.004	37.45 ± 24.49	0.23

* p-value for comparison to Caucasian group, including adjustment for the stratification variable birth weight (continuous form) and the following baseline characteristics: gestational age, CRIB score, gender, ethnicity, maternal education and household income.

DISCUSSION:

The primary purpose of this study was to better understand early working memory in 18 – 22 month olds born ELBW by examining the association between object permanence and self regulation (i.e., emotional and attentional regulation) as well as the impact of ethnicity, gender, illness severity, and family socio-economic status on object permanence performance. We found that object permanence mastery was highly correlated with measures of self-regulation, indicating that emotional and attention regulation difficulties in children born ELBW are associated with poorer performance on measures of early working memory such as object permanence tasks. In addition we found a significant gender difference in object permanence mastery, with girls having twice the likelihood of achieving higher levels of object permanence than boys. Contrary to our expectations, medical illness severity and family socio-economic variables were not significantly associated with object permanence mastery. As we hypothesized, object permanence performance was not impacted by ethnicity or race, in contrast to MDI scores, which were significantly affected by race and ethnic group.

Piaget first identified different types of early problem solving skills that were developmental in nature when he wrote about sensori-motor and concrete operational skills in toddlers (Piaget, 1953). Using his theory, tasks were created to measure early reasoning skills in preschoolers that were associated with prefrontal cortex cognitive deficits such as the A not B test (Diamond, 1997). Similar tasks of object permanence are imbedded within traditional tests of infant intelligence, such as the Bayley Scales of Infant Development (1985), though these tasks have not been studied separately as a

measure of working memory, at 18-22 months in children born ELBW. Recently several studies have examined at working memory as a measure of executive functioning in school age outcome studies for children born preterm (Curtis et al, 2002; Luciana, Lindeke, & Georgieff, 1999). Woodward et al (2005) found that two year old children born preterm compared to those born at term, had difficulty encoding new information in working memory. On MRI scan, children born preterm had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parietooccipital and premotor areas). Expanding such research to infants and younger children would be beneficial, as it has been well documented that the Bayley Scales of Infant Development, frequently used as an outcome measure for neonatal studies, is a poor predictor of later cognitive function (Hack et al, 2005).

As defined by Goldman-Rakic (1987) working memory is a process that involves holding task relevant information in mind for brief intervals so that the information can be used to guide future actions. Interconnections between the frontal cortex, caudate nucleus and hippocampus have been found to be integral for working-memory function (Alexander et al, 1986; Goldman-Rakic, 1987). Researchers have been trying to better understand factors related to school failure and success, in children born preterm (Nelson et al, 2002; Luciana, et al. 1999) Studies looking at working memory, executive function and CNS imaging in infants and toddlers born ELBW may help link functional and structural knowledge of specific learning and self-regulatory problems that develop with infants born preterm. Aylward (2005) summarized that 'executive function deficits may be subtle, though they could have substantial impact on cognitive, social and academic functioning' (pg. 434). In addition, deficits in skills related to executive function have

been found to affect attention and self-regulation; for example ADHD has been found to occur 2.6 to 4 times more frequently in children born very low or extremely low birth weight (Whitaker, Van Rosen and Feldman, 1997), 60 to 70% of ELBW children have been reported to require special assistance in school (Saigal, den Ouden, & Wolke, 2003). Early identification of learning and self-regulatory differences in this population may permit utilization of early intervention techniques to ameliorate these school-age problems.

The effect of gender on tests of working memory has not been reported; however, gender has been found to affect (Luciana, 1999; Anderson et al, 2004) measures of cognition in 18-22 month olds born both VLBW and ELBW (Hoekstra et al, 2004; Hintz et al, 2006). For example Hack et al (2000) found that male gender was a significant predictor of a subnormal MDI score with an odds ratio of 2.73. In addition a study of school age children found that 11 year old boys born preterm at had a three to six fold increase in learning disorders compared to controls (Johnson et al, 2000). Such differences have also been noted in young children born VLBW, though Luciana (1999) proposed that NICU survivors have a developmental delay in brain maturation, which could be greater in boys as indicated by our findings.

The impact of ethnicity on intelligence testing has been explored since the 1960's when Arthur Jensen began the scholarly debate on race and intelligence. Outcome studies have been mixed with some indicating that maternal race added prognostic information to poorer developmental outcome (Schmidt et al 2003), though others attributed differences to socioeconomic status (Lowe et al, 2005), maternal education (Laptook et al, 2005) or nonwhite race (Hoekstra, et al, 2004, Vohr, 2005). Findings regarding differences in

specifically nonwhite race groups were mainly on tests of intelligence such as the Wechsler Preschool and Primary Scale of Intelligence-Third (WIPPSI-III) (Wechsler,2002) or the Bayley Scales of Infant Development. Our findings that the working memory items from the Bayley Scales of Infant Development II were not different between ethnic groups, while the MDI score was, provides an additional reason to explore measures of working memory and other executive function as more ethnically unbiased in contrast to tests of cognition.

Limitation of our study include the lack of a term control group and the small numbers within our ethnic groups, especially Hispanics and Asians. In addition, the items of object permanence were taken from the Bayley Scales of Infant Development and did not have the increasing delays required to find an item, that the A not B task requires. These items were also part of the overall MDI score, though they only represented 3 of over 25 items generally administered.

Further studies examining ways to better assess working memory in children born ELBW at young ages, including the first year of life, could assist in better identification of those children at greater risk for later attention and learning problems. Measures of working memory should be included in future studies that measure developmental outcome, allowing us to go beyond measures of cognition which can be ethnically biased. Research expanded to better understand brain-behavior relationships of early pre-frontal skills in this vulnerable population could improve our ability to intervene earlier when working with children born ELBW.

NICHD HD38540.

CRIB REFERENCE: The International Neonatal Network. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet* 1993;342 : 193-98

Date: November 30, 2007

To: Neonatal Research Network Follow-up Committee, Betty Vohr, Chair

From: Jean Lowe Ph.D. and Janell Fuller, MD
University of New Mexico

Re: Proposal for ancillary study to the SUPPORT trial, "Evaluation of early working memory in extremely preterm infants"

Synopsis: We propose to study early working memory in extremely preterm infants enrolled in the NICHD SUPPORT trial by recording and analyzing responses to 3 specific items from the Bayley Scales of Infant Development-III (2006) (Bayley-III), which measure object permanence (items 40, 45 and 50), and evaluating the relationship of "mastery of object permanence" to performance on the Bayley-III at 18 – 22 months, to MRI findings at term gestation, and to performance on tests of executive function at 6 – 7 years of age.

Our specific **hypotheses** are that:

- infants born extremely preterm (<28 0/7 weeks) who achieve object permanence mastery will do significantly better on the Bayley-III test of Cognition and Language at 18-22 months than those who do not.
- in contrast to Bayley Cognitive and Language scores, object permanence mastery at 18 months will **not** be affected by SES or ethnic grouping.
- children who achieve object permanence mastery will have significantly **fewer** abnormal findings on the MRI performed at term as part of the SUPPORT trial.

- children who obtain object permanence mastery will perform significantly better on tests of executive function at 6 and 7 years.

Background and significance:

Research related to Executive Function: Executive function is an umbrella term that encompasses three main areas: working memory, inhibition and cognitive flexibility (Davidson, Amso, Anderson & Diamond, 2005). Recently we have seen more studies that look at working memory as a measure of executive functioning in school age outcome studies (Anderson, et al, 2004; Curtis et al, 2002; Luciana, Lindeke, & Georgieff, 1999) with significant differences found between executive functioning in those children born preterm in comparison to children born at term. Studies have shown executive function deficits in children school-aged and older who were born prematurely (Anderson, & Doyle, 2004), which persist even after taking IQ differences into account (Bayless & Stevenson, 2007).

In one of the few studies of executive function with young children born preterm Woodward et al (2005) found that 2 year olds born preterm in comparison to those born at term, had difficulty encoding new information in working memory, and on MRI children born preterm had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parietooccipital and premotor areas). Studying these vulnerable populations at younger ages could result in executive function interventions that could be clinically useful. New measures have recently been developed which allow researchers to tap into the foundations of executive function in very young children, particularly their working memory, impulse control, and

rule use (Carlson, 2005). Although these new measures for preschool children have been employed with typically developing populations (Carlson, 2005) there are currently very few studies investigating executive function in preschool children born prematurely. The few studies that have been conducted found that preschoolers born VLBW without major neurological deficits may have specific difficulty in sustained attention, visuospatial processing, and spatial working memory when compared with full term children matched for chronological age and IQ (Vicari, Caravale, & Carlesimo, 2004).

A recent randomized trial of early hydrocortisone treatment (Watterberg et al, 2007) found that fewer hydrocortisone-treated patients had a Bayley-II MDI of <70 and that more of the hydrocortisone-treated children showed evidence of awareness of object permanence on the Bayley-II. Further investigation indicated that MDI scores were significantly higher in the white ethnic group while object permanence mastery was relatively similar across all ethnic groups (Blacks, Hispanics, Asians, whites). (Lowe et al, manuscript in preparation and attached).

Our finding that object permanence mastery is not impacted by either ethnic group or income is relevant to how we could improve our way of identifying those children 'at-risk' for later developmental sequelae, as the Bayley Scales MDI, frequently used in research as an outcome measure, is a poor predictor of later cognitive function (Hack et al, 2005). Object permanence items as a measure of early working memory (Diamond, et al. 1997) have been related to the development of prefrontal cortical function (Woodward, et al.2005) and the earliest measure of reasoning skills in toddlers. This is relevant to intervention techniques that can be developed to specifically work on tasks that could enhance these skills. In conjunction with the Bayley Scales cognitive

score, use of a measure of object permanence may also improve our detection of ongoing problems with executive function at 18-22 months, which is highly related to later learning difficulties.

Study design: We propose to separately record items 40, 45 and 50 from the Bayley-III Cognitive Scale in infants enrolled in the SUPPORT trial, and to analyze the relationship of 'mastery of object permanence', defined as achievement of two of these items, to (1) MRI findings at term gestation (done for the imaging secondary of the SUPPORT trial; (2) Bayley-III Cognitive scale and factors affecting performance on both the cognitive scale and object permanence achievement; and (3) tests of executive function at 6 and 7 years within the proposed long-term follow up study of infants enrolled in the SUPPORT trial.

This ancillary study cannot be deferred until the long-term follow up study for SUPPORT is either approved or disapproved, because children in the SUPPORT trial are beginning to enter the 18 – 22 month window. This study would be easy to add on, as it would only require extracting results from the Bayley-III Cognitive Scale and recording them for data collection. If the 6 – 7 year follow up is not approved, collecting these data will still be valuable in assessing the relationship of mastery of object permanence to MRI findings and to Bayley performance in a large cohort of extremely preterm infants.

Budget: The budget would only require (1) a minimal increase in data collection and entry time and (2) statistical analysis. Bayley examiners can fill in the coding sheet noting specific performance on these items at the time the test is performed and scored. No additional testing, equipment or training is required.

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Reasons for Late Surfactant Administration Provided on Form SUPP06

Data as of March 27, 2008

Treatment assignment	Reason for late surfactant administration, from SUPP06	Surfactant timing (hours post-birth)
CPAP	Infant required intubation in delivery room for resuscitation. Failed to receive surfactant in NICU. Extubated to NSIMV at approximately 9 hours of age.	
CPAP	Infant intubated in DR, self extubated enroute to NICU prior to surf being given.	
CPAP	Faculty unaware of requirement, research RN not in-house.	
CPAP	Surfactant not given. RT was unaware that all infants in the study who are intubated should receive surfactant. Stated that FiO2 wasn't high enough to give surfactant. RT's were told all infants who require intubation on the study should receive surfactant.	
CPAP	Staff waited for chest x-ray to determine ETT placement before giving survanta. Tech was slower than expected arriving to NICU. Staff reminded that did not need x-ray for ETT placement before giving Survanta.	1.3
CPAP	Unsure of ETT placement - x-ray performed, tube repositioned, then surfactant administered.	1.4
CPAP	Surfactant administration was slightly delayed due to the timing of admission to the NICU (at RN and RT shift change) and multiple unsuccessful attempts at placing a peripheral IV. Surfactant is given back in the NICU at university hospital (not in delivery room).	1.5
Surfactant	Discrepancy with MFM Fellow's date for GA. Intubation & Surfactant held off until GA clarified.	1.2
Surfactant	Chest x-ray and admission procedures delayed the administration of first dose of surfactant.	1.3
Surfactant	Staff did not realize infant was to be randomized into the trial until she arrive to NICU. Surfactant administration was delayed due to delay in randomization, necessity of checking a chest x-ray for ET tube placement, and change out of a malfunctioning isolette.	1.3
Surfactant	Randomization envelope for correct gestational age was not in resus. bag. Pulled cart after arriving in unit. Intubated at 56 minutes of life. Survanta given 35 minutes later.	1.5
Surfactant	Unable to stabilize infant on ventilator. Hand bagging and infant's saturations very labile. Sats ranging 38% - 83%.	1.5
Surfactant	Surfactant was given at 1 hour and 32 minutes of life, after admitting procedures were completed and ETT position was confirmed by chest x-ray.	1.5
Surfactant	Infant was a difficult delivery and required a great deal of support during resuscitation. Lines and x-ray were completed at around 1 hour of life.	1.6
Surfactant	Infant intubated with audible air leak; CVR taken and tube pulled back before surfactant administration.	1.6
Surfactant	Surfactant administration occurred at 1 hour and 44 minutes of life, after admitting procedures were completed and ETT position was confirmed by chest X-ray.	1.7
Surfactant	Breath sounds unclear after intubation in DR and CXR was ordered to verify placement of ETT. Survanta given at 1 hr 52 minutes.	1.8
Surfactant	Miscommunication among RRT and MD re: assignment compounded by critical status of other babies in unit delayed intubation and surfactant administration, surfactant administered at 2 hours of age.	2.1
Surfactant	Infant was hypoglycemic and staff was attempting to get IV access before giving survanta. Neonatal fellow didn't feel comfortable giving survanta while infant was covered with drapes and he couldn't see infant.	2.2
Surfactant	Infant intubated after consent delay -- required translator. After consent obtained, infant intubated, then arterial line put in, then surfactant given.	2.6
Surfactant	Twin admission -- other twin coded and died -- not enough personnel to give surfactant within 1 hour. Surfactant given as soon as possible.	2.7
Surfactant	Baby doing well enough immediately following delivery that MDs felt baby did not initially require intubation although that was the randomization assignment.	3.4

Late surfactant for infants assigned to CPAP (not reported on SUPP06)

The FREQ Procedure

Center ID number		
CENTER	Frequency	Cumulative Frequency
3	4	4
4	1	5
8	2	7
12	1	8
13	1	9
14	5	14
15	2	16
16	2	18
18	1	19
19	1	20
23	1	21
24	3	24
25	1	25
26	1	26

From:	Huitema, Carolyn Petrie
To:	Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; wcarlo@peds.uab.edu; mcw3@cwru.edu; bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Poole, W. Kenneth; Gantz, Marie; wrich@ucsd.edu
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; fmartinez@ucsd.edu; msumner@peds.uab.edu; Brenda Vecchio; Sunkara, Geeta S.
Subject:	RE: Reminder: SUPPORT Conference Call
Date:	Thursday, April 03, 2008 3:34:34 PM
Attachments:	SUPPORT call 2080403.pdf

Dear all-

Attached are the minutes from the SUPPORT subcommittee conference call.

These will be posted on the NRN private website

- Administration\Minutes\Subommittee Minutes\SUPPORT
- As "April 1, 2008"

Thank you,
Carolyn

RTI INTERNATIONAL | **Memorandum**

DATE: April 1, 2008

TO: NRN SUPPORT Subcommittee

FROM: RTI International
Data Coordinating Center

RE: SUPPORT Subcommittee Conference Call Minutes

Participants: Drs. Finer, Gantz, Faix, Yoder, Schibler, Goldberg, Walsh, Carlo, Higgins, Laptook, Das. Ms. Cunningham, Zaterka-Baxter, Newman, Huitema.

Study Status
The group reviewed enrollments to date, adverse events, and protocol deviations.

Currently there are 990 infants enrolled which is 76% of total. Completion will take another 9-11 months for enrollment then 4-5 months before the data entry is closed. Expect the DSMC review at 75% of study outcomes will be late summer 2008.

The adverse events are lower than baseline in all categories but the NRN baseline may have also moved lower. The only adverse event for which the SUPPORT rate is not lower is air leak.

Protocol Deviations
The most common protocol deviation is failure to use study oximeter at times required by protocol and next is failure to administer surfactant within first hour of life. For most centers, the number of protocol deviations is ≤25% of the number of infants enrolled.

Surfactant delivered > 1hr of intubation: Dr. Finer asked for scenarios/discussion (10 centers/28 deviations). There is a 10 minute grace period outside the 1 hr window. Dr. Gantz will look to see how long outside the hour of delivery surfactant is actually given. Centers will be queried if needed. This may be due to Center practice of stabilization and line placement with verification prior to surfactant treatment.

Dr. Gantz has removed the HFNC use within the first 14 days of study from the protocol deviation/violation reports and is generating a separate report monitoring HFNC use for CPAP infants in the first 14 days of life.

Compliance with Target SpO2 Ranges
Centers are staying within an acceptable range for saturations – if data continues, the study arms should continue to have good separation. Dr. Finer feels that this is acceptable for safety. Dr. Carlo added that it is difficult to keep within the narrow range but current the data reports looks okay.

Oximeter Issues
Masimo had some changes to their software for leap year. For oximeters in use when the year changed from 2007 to 2008, this caused 24 hours worth of repeated data to be instantaneously inserted into the pulse oximeter memory early on the morning of January 1. Once the oximeters were turned off and on, the problem corrected itself; this affected 27 cases but as of 03/31/08, RTI knows how to correct the data for this problem. The problem did not affect the oximeter

function, just the downloads. There were problems with Satshare in UK; may have been a cable. New Mexico experienced problems that have hopefully been fixed by replacing the malfunctioning oximeters (alarming when in correct saturation range; erratic values)

Secondaries

- MRI S Hintz to report – Discuss Longer Term follow-up
  - Dr. Hintz's protocol is going to the SC for a vote. NHLBI would like to follow these kids longer but currently does not have the funding to support this project.
- Breathing Outcomes
- Nutrition
- Antenatal consent

New Mexico Ancillary

An ancillary study submitted by New Mexico focuses on Working Memory and MRI. Dr Finer's main concern is that this study is not linked to the hypotheses in SUPPORT. His understanding is that any Ancillary/Secondary should have such a link as the population will be potentially affected in any outcome measure by the randomized interventions. The center should also work with the Follow Up PI in developing this protocol. The authors propose to use three of the Bayley cognitive items at the 18 month visit. Since this data is not logged into the DMS (only the Bayley summary scores, not individual items), sites must go back to the paper records then record in the DMS. Also, there is no sample size calculation. The proposal needs a budget (cost to go back, retrieve scores, data entry). There needs to be clarification of the test being used to evaluate executive function, who is doing it, who is paying for it etc.

There could be a potential link to Dr. Hintz's study but it is not clearly delineated in the protocol. This study is not contingent on whether or not the SC approves Dr. Hintz's study.

Review of Executive Function proposal

Review 1:
The study needs a hypothesis and sample size. The SUPPORT Hypotheses and randomization need to be discussed as either potential confounders or as incorporated into their hypotheses. The need to specify the actual work required to get and transmit the data and the associated costs The evaluation for executive function at 6-7 years was not stated and needs to be described and the associated costs and time etc. Is the study linked to the MRI Extension?

Review 2:
The proposed ancillary to SUPPORT includes a plan to evaluate the relationships between components of the Bayley and performance on tests of executive function at 6-7 years of age. However, the protocol does not specify which executive function tests will be performed and if they are all part of the proposed 6-7 year follow up. If they are not part of the proposed follow-up, the feasibility of doing the additional testing should be cleared with the follow-up PIs. (additional visit time, training, etc.)

Review 3:
1. There should be a stronger rationale for why this study is being proposed. The accompanying article seems to have done this already. Would this work just repeat what was already done or does it expand the field?
2. There is no sample size. SUPPORT has currently enrolled 990 pts of projected 1300- is it proposed that this will be done prospectively, with the separate items for object permanence collected at the time of administration, or are the authors requesting that centers go back to the original source documents and collect the data.
3. Is this work proposed only if the 6-7 yr follow up is approved?
4. Budget estimates are needed.

Prospective Meta-Analysis
Data Sharing with NeoProm ie Enrollments, consents, oximeter compliance.

This group will meet in Hawaii. Dr. Gantz plans to attend. They requested information on our study, and if the steering committee approves at the April 2008 meeting we will send SUPPORT enrollment, protocol, manual and forms, DMSC roster and minutes (sanitized). They also want percent of parents approached for consent. Dr. Finer will follow up with Mr. Rich to send a copy of his presentation on antenatal consent.

Other Issues
New Mexico experienced problems with the orange oximeters (as described above). The 5 malfunctioning oximeters were sent back to Massimo who will replace/repair them. The oximeters were alarming when in appropriate range and were showing erratic sats on stable infants (compared with non-study oximeter placed for safety reasons).

Extended situation at NM: A mother was admitted for delivery of at 25weeks; NM had no orange oximeters but new 4 had been sent for delivery next day. A decision was made by Drs. Finer and Higgins to have NM consent and randomize an infant, knowing they would have oximeters sent the next day if randomized to orange. If randomized to orange, this would have been considered to be a protocol violation (not on oximeter w/in 2 hrs) but not considered ineligible (equipment not available). The SC approved this course of action.

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kris Zaterka-Baxter
Subject: Re: SUPPORT AE
Date: Thursday, April 03, 2008 11:15:49 AM

Kris and Rose,
After I spoke to Pablo, he told me the other twin also had a pulmonary hemorrhage and Grade III IVH. I'll be working on that Med Watch too. These are not related to the study. The NN# is(b) (6)
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From: Gantz, Marie
To: Finer, Neil
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Late surfactant administration for SUPPORT infants
Date: Wednesday, April 02, 2008 5:42:47 PM
Attachments: Late surf for CPAP by center 3-27-08.rtf
Late surf reasons from SUPP06 3-27-08.doc

Neil,

In response to questions yesterday in the SUPPORT subcommittee meeting, here is some additional information on protocol deviations pertaining to late surfactant administration.

The 37 protocol deviations reported in the SUPPORT update (9 cases before January 1, 2006, and 28 cases after) include all protocol deviations for late surfactant entered on SUPP06, and additional deviations for the surfactant treatment group that were not reported on SUPP06 but were found using forms SUPP03 and SUPP04. Protocol deviations reported on the SUPP06 were for 29 infants assigned to surfactant and 8 infants assigned to CPAP. There were 4 cases reported on SUPP06 in which surfactant was not given at all; those babies were assigned to CPAP. In the remaining cases, surfactant was given at 1.2 – 3.4 hours post-birth, with a median time of 1.6 hours. Reasons for the deviations (when provided on SUPP06) are listed in the attached document.

In addition to the 37 deviations included in the SUPPORT update, there are 26 additional cases in which infants assigned to CPAP were intubated in the DR but received surfactant after 1 hour of life. In those cases, surfactant was given at 1.2 – 3.2 hours, with a median of 1.8 hours. The number of cases by center is attached. Please let me know if you would like RTI to ask the centers to enter protocol deviations for the cases. I apologize for not including these deviations in the SUPPORT update; when I originally looked at late surfactant use on the SUPP03 and SUPP04 I was focusing only on the infants assigned to surfactant.

Let me know if you have any questions or would like additional information.

Marie

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

Late surfactant for infants assigned to CPAP (not reported on SUPP06)

The FREQ Procedure

Center ID number		
CENTER	Frequency	Cumulative Frequency
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Reasons for Late Surfactant Administration Provided on Form SUPP06

Data as of March 27, 2008

Treatment assignment	Reason for late surfactant administration, from SUPP06	Surfactant timing (hours post-birth)
CPAP	Infant required intubation in delivery room for resuscitation. Failed to receive surfactant in NICU. Extubated to NSIMV at approximately 9 hours of age.	
CPAP	Infant intubated in DR, self extubated enroute to NICU prior to surf being given.	
CPAP	Faculty unaware of requirement, research RN not in-house.	
CPAP	Surfactant not given. RT was unaware that all infants in the study who are intubated should receive surfactant. Stated that FiO2 wasn't high enough to give surfactant. RT's were told all infants who require intubation on the study should receive surfactant.	
CPAP	Staff waited for chest x-ray to determine ETT placement before giving survanta. Tech was slower than expected arriving to NICU. Staff reminded that did not need x-ray for ETT placement before giving Survanta.	1.3
CPAP	Unsure of ETT placement - x-ray performed, tube repositioned, then surfactant administered.	1.4
CPAP	Surfactant administration was slightly delayed due to the timing of admission to the NICU (at RN and RT shift change) and multiple unsuccessful attempts at placing a peripheral IV. Surfactant is given back in the NICU at university hospital (not in delivery room).	1.5
Surfactant	Discrepancy with MFM Fellow's date for GA. Intubation & Surfactant held off until GA clarified.	1.2
Surfactant	Chest x-ray and admission procedures delayed the administration of first dose of surfactant.	1.3
Surfactant	Staff did not realize infant was to be randomized into the trial until she arrive to NICU. Surfactant administration was delayed due to delay in randomization, necessity of checking a chest x-ray for ET tube placement, and change out of a malfunctioning isolette.	1.3
Surfactant	Randomization envelope for correct gestational age was not in resus. bag. Pulled cart after arriving in unit. Intubated at 56 minutes of life. Survanta given 35 minutes later.	1.5
Surfactant	Unable to stabilize infant on ventilator. Hand bagging and infant's saturations very labile. Sats ranging 38% - 83%.	1.5
Surfactant	Surfactant was given at 1 hour and 32 minutes of life, after admitting procedures were completed and ETT position was confirmed by chest x-ray.	1.5
Surfactant	Infant was a difficult delivery and required a great deal of support during resuscitation. Lines and x-ray were completed at around 1 hour of life.	1.6
Surfactant	Infant intubated with audible air leak; CVR taken and tube pulled back before surfactant administration.	1.6
Surfactant	Surfactant administration occurred at 1 hour and 44 minutes of life, after admitting procedures were completed and ETT position was confirmed by chest X-ray.	1.7
Surfactant	Breath sounds unclear after intubation in DR and CXR was ordered to verify placement of ETT. Survanta given at 1 hr 52 minutes.	1.8
Surfactant	Miscommunication among RRT and MD re: assignment compounded by critical status of other babies in unit delayed intubation and surfactant administration, surfactant administered at 2 hours of age.	2.1
Surfactant	Infant was hypoglycemic and staff was attempting to get IV access before giving survanta. Neonatal fellow didn't feel comfortable giving survanta while infant was covered with drapes and he couldn't see infant.	2.2
Surfactant	Infant intubated after consent delay -- required translator. After consent obtained, infant intubated, then arterial line put in, then surfactant given.	2.6
Surfactant	Twin admission -- other twin coded and died -- not enough personnel to give surfactant within 1 hour. Surfactant given as soon as possible.	2.7
Surfactant	Baby doing well enough immediately following delivery that MDs felt baby did not initially require intubation although that was the randomization assignment.	3.4

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
Subject: RE: SUPPORT AE
Date: Wednesday, April 02, 2008 5:41:38 PM

We have a SUPPORT baby who had a pretty bad course and was removed from the ventilator today. NN# is(b) (6). Adverse events include, pneumothorax, PIE, bilateral Grade III IVH, pulmonary hemorrhage and death. Med Watch is pending and AEs are not related to the study.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From: Huitema, Carolyn Petrie
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: SUPPORT call minutes
Date: Tuesday, April 01, 2008 4:54:32 PM
Attachments: SUPPORT con call 2080401.doc

Hi-

Please review the attached minutes from today's SUPPORT call.

Thanks!

Carolyn Huitema

Research Analyst
RTI International
(301) 270-6664
petrie@rti.org

RTI INTERNATIONAL | **Memorandum**

DATE: April 1, 2008

TO: NRN SUPPORT Subcommittee

FROM: RTI International
Data Coordinating Center

RE: SUPPORT Subcommittee Conference Call Minutes

Participants: Drs. Finer, Gantz, Faix, Yoder, Schibler, Goldberg, Walsh, Carlo, Higgins, Laptook, Das. Ms. Cunningham, Zaterka-Baxter, Newman, Newman, Huitema

Study Status
The group reviewed enrollments to date, adverse events, and protocol deviations.

Currently 990 per August > 75% of total, completion will take another 9-11 months for enrollment then 4-5 months before the ~~book get~~ data entry is closed. Expected the DSMC review at 75% will be late summer

The adverse events are lower than baseline in all categories but the NRN baseline may have also moved lower. The only area not lower, but not higher by any significant amount, is the air leak information.

The commonest protocol deviation is failure to use the study oximeter and next is the timing of surfactant.

Marie has removed the HFNC use and separately indicated its use

Protocol deviation by center would be interesting (use of HFNC is still present but not considered a deviation currently). Center 24 has a higher level of deviation.

Surfactant delivered > 1hr of intubation: Dr. Finer asked for scenarios/discussion (10 centers/28 deviations). There is a 10 minute grace period outside the 1 hr window. Dr. Gantz will look to see how long outside the hour the delivery of surf actually is occurring. Centers can be queried if needed. This may be due to Center practice of stabilization and line placement with verification prior to surfactant treatment.

Staying w/in an acceptable range for saturations – if data continues, should continue to have good separation. Feel that this is acceptable for safety. Expect to get good separation. Dr. Carlo added that it is difficult to keep within the narrow range but looks okay.

Oximeter Issues
Masimo had some change to their hard/soft ware for leap year. This caused extraneous data and uploaded a 24 hr repeat of data that immediately occurred. As soon as the oximeters were turned off and on, the problem corrected itself; this affected 27 cases but as of 03/31/08, RTI knows what and how to fix this problem. This problems did not affect the oximeter function, just the downloads. Problems with Satshare in UK; may have been a cable. New Mexico experienced

problems that have hopefully been fixed by replacing the malfunctioning oximeters (alarming when in correct saturation range)

Secondaries

- MRI S Hintz to report – Discuss Longer Term follow-up
  - Dr. Hintz's protocol is going to SC for a vote. NHLBI would like to follow these kids longer but does not have money to fund this project at this time.
- Breathing Outcomes
- Nutrition
- Antenatal consent

New Mexico Ancillary

An ancillary study submitted by New Mexico focuses on Working Memory and MRI. Dr Finer's main concern is that this study is not linked to the hypotheses in SUPPORT. His understanding is that any Ancillary/Secondary should have such a link as the population will be potentially affected in any outcome measure by the randomized interventions. The center should also work with the Follow Up PI in developing this protocol. The authors propose to use three of the Bayley cognitive items at the 18 month visit. Since this data is not logged into the DMS (only the Bayley summary scores, not individual items), sites must go back to the paper records then record in the DMS. Also, there is no sample size calculation. The proposal needs a budget (cost to go back, retrieve scores, data entry). There needs to be clarification of the test being used to evaluate executive function, who is doing it, who is paying for it etc.

There could be a potential link to Dr. Hintz's study but it is not ~~spelled out~~clearly delineated in the protocol. This study is not contingent on whether or not the SC approves Dr. Hintz's study.

Dr. Higgins asked the group to send her comments on this proposal.

Prospepective Meta-Analysis

Data Sharing with NeoProm ie Enrollments, consents, oximeter compliance.

This group will meet in Hawaii. Dr. Gantz plans to attend. They requested many items and will send: SUPPORT protocol and forms, DMSC roster and minutes (sanitized). They also want percent of parents approached for consent. Dr. Finer will follow up with Mr. Rich to send a copy of his presentation on antenatal consent.

Other Issues

New Mexico experience problems with the orange oximeters and sent back to Massimo. The oximeters were alarming when in appropriate range. When NM had no orange oximeters; scenario approved by SC ie; to consent and randomize an infant, knowing they would have oximeters sent the next day if randomized to orange. This would be a protocol violation (not on oximeter w/in 2 hrs) but not considered ineligible (equipment not available).

From: Wally Carlo, M.D.
To: Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.; mcw3@cwru.edu; bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Poole, W. Kenneth; Gantz, Marie; wrich@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; fmartinez@ucsd.edu; Brenda Vecchio
Subject: RE: Reminder: SUPPORT Conference Call
Date: Tuesday, April 01, 2008 4:18:16 PM

Rose:

Here are my comments on the proposed ancillary working memory study.

The proposed ancillary to SUPPORT includes a plan to evaluate the relationships between components of the Bayley and performance on tests of executive function at 6-7 years of age. However, the protocol does not specify which executive function tests will be performed and if they are all part of the proposed 6-7 year follow up. If they are not part of the proposed follow-up, the feasibility of doing the additional testing should be cleared with the follow-up PIs.
(additional visit time, training, ect.)

Hope this helps

Wally Carlo, M.D.
University of Alabama at Birmingham
Edwin M. Dixon Professor of Pediatrics
Director, Division of Neonatology
Director Newborn Nurseries
525 New Hillman Building
Birmingham, Alabama 35233
Phone: 205 934 4680
Direct Line: 205 934 9196
Cell Phone: 205 266(b) (6)
FAX: 205 934 3100

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, April 01, 2008 9:20 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.; mcw3@cwru.edu; bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nancy newman; Poole, W. Kenneth; Gantz, Marie; wrich@ucsd.edu
Cc: archerst@mail.nih.gov; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; fmartinez@ucsd.edu; Marsha Sumner; Brenda Vecchio
Subject: Reminder: SUPPORT Conference Call

Reminder for today's call.

Tuesday, April 1st
SUPPORT 3:00-4:30pm ET

For all calls please dial

Within the USA
866-675(b) (6)
or
Outside the USA
1-203-310(b) (6)
Then, enter Participant Passcode:

(b) (6)

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, March 28, 2008 1:45 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject: FW: SUPPORT updates

Hi Everyone
Here is an agenda for next weeks phone meeting, and the updates from Marie. Thanks Marie for getting this data to us.

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations (Currently 990 per August > 75% of total, completion will take another 9-11 months for enrollment)
The adverse events are lower than baseline in all categories but the NRN baseline may have also moved lower. The only area not lower, but not higher by any significant amount is the air leak information
The commonest protocol deviation is failure to use the study oximeter and next is the timing of surfactant.
Marie has removed the HFNC use and separately indicated its use

2. Discuss any oximeter issues – concerns regarding Sat Share from UK trial, and New Mexico oximeters, and any data loss from Masimo software/hardware

3. Review status of Secondaries-
MRI S Hintz to report – Discuss Longer Term follow-up
Breathing Outcomes - See Tim's report - Attached
Nutrition
Antenatal consent

4. Discuss Ancillary – New Mexico Working Memory and MRI (Attached) – My main concern is that this study is not linked to the hypotheses in SUPPORT. My understanding is that any Ancillary/Secondary should have such a link as the population will be potentially affected in any outcome measure by the randomized interventions.

5. Data Sharing with NeoProm – The prospective Meta Analysis – ie Enrollements, consents, oximeter compliance.
6. Other Issues

Please let me know if there are additional issues you would like added to the agenda

Neil

Neil N. Finer, M.D.
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Director, Division of Neonatal-Perinatal Medicine
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UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759

Facsimile: 619.543.3812

From:	Finer, Neil
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	RE: SUPPORT updates
Date:	Tuesday, April 01, 2008 3:43:26 PM

Hi Rose
We discussed the issues of the Ancillary regarding Executive Function from New Mexico. The concerns that were raised were as follows:
The study needs a hypothesis and sample size
The SUPPORT Hypotheses and randomization need to be discussed as either potential confounders or as incorporated into their hypotheses.
The need to specify the actual work required to get and transmit the data and the associated costs
The evaluation for executive function at 6-7 years was not stated and needs to be described and the associated costs and time etc.
Is the study linked to the MRI Extension?
I hope this covers what we discussed.
Neil

From: Finer, Neil
Sent: Friday, March 28, 2008 10:45 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade
Subject: FW: SUPPORT updates

Hi Everyone
Here is an agenda for next weeks phone meeting, and the updates from Marie. Thanks Marie for getting this data to us.

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations (Currently 990 per August > 75% of total, completion will take another 9-11 months for enrollment)
The adverse events are lower than baseline in all categories but the NRN baseline may have also moved lower. The only area not lower, but not higher by any significant amount is the air leak information
The commonest protocol deviation is failure to use the study oximeter and next is the timing of surfactant.
Marie has removed the HFNC use and separately indicated its use

2. Discuss any oximeter issues – concerns regarding Sat Share from UK trial, and New Mexico oximeters, and any data loss from Masimo software/hardware

3. Review status of Secondaries-
MRI S Hintz to report – Discuss Longer Term follow-up
Breathing Outcomes - See Tim's report - Attached
Nutrition
Antenatal consent

4. Discuss Ancillary – New Mexico Working Memory and MRI (Attached) – My main concern is that this study is not linked to the hypotheses in SUPPORT. My understanding is that any Ancillary/Secondary should have such a link as the population will be potentially affected in any outcome measure by the randomized interventions.

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compliance.
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From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Barbara Stoll; Ira Adams-Chapman; Das, Abhik; Gantz, Marie
Subject: Re: SUPPORT
Date: Monday, March 31, 2008 4:53:49 PM

Here is the follow-up for our SUPPORT children:

CENTER	NETWORK	ROP_message
9	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. *Exam has been done and we are awaiting report.*
CENTER	NETWORK	FU_message
9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed ***This child was finally seen today--family came from the Florida/Georgia line. All items for exam have been completed.***
9	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed *Bayley completed on 2/29 and awaiting report to enter.*

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Bridge, Renee
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: support data
Date: Friday, March 28, 2008 1:52:20 PM

I have entered the information for SUPP 10 for patient (b) (6) Thank you for the update. Hope all is well.
Renee Bridge, UCSD

From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	FW: SUPPORT updates
Date:	Friday, March 28, 2008 1:46:26 PM
Attachments:	SUPPORT Enrollment 3-27-08.doc SUPPORT Adverse Events 03-27-08.doc SUPPORT Use of HFNC 03-27-08.doc SUPPORT Protocol Deviations - old vs new 03-27-08.doc SUPPORT Protocol Deviations by center - old vs new 03-27-08.doc All Centers pct in range through Mar08.rtf Breathing Outcomes Update-April 08.doc Working Memory in ELBW 12-1-07 (2).doc Proposal for ancillary study to Support Trial Working Memory(2).doc

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SUPPORT Enrollment as of March 27, 2008

Total Enrolled

	N	% of total (1310)
Enrolled	990	76%

Enrollment by Center

Center	<Oct-07	Oct-07	Nov-07	Dec-07	Jan-08	Feb-08	Mar-08	Total
3	71	4	3	1	2	3	4	88
4	44	1	1	0	0	1	5	52
5	30	3	3	3	4	1	2	46
8	17	0	0	0	0	0	0	17
9	57	2	0	0	1	0	2	62
11	62	1	2	0	5	0	0	70
12	48	1	2	2	2	2	1	58
13	20	0	1	0	4	0	0	25
14	78	0	1	3	6	2	5	95
15	30	0	3	1	0	1	2	37
16	108	4	6	6	9	2	8	143
18	58	0	2	2	0	1	1	64
19	41	4	1	3	2	0	0	51
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	52	1	3	0	0	1	0	57
23	37	1	1	1	0	1	1	42
24	11	1	4	1	1	2	0	20
25	26	1	2	0	0	1	4	34
26	8	2	0	0	1	0	1	12
Total	815	26	35	23	37	18	36	990
Centers		17	17	17	17	17	17	
Avg/center		1.5	2.1	1.4	2.2	1.1	2.1	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	9
2.5	8
3	6

Percent of SUPPORT infants with selected adverse events as of March 27, 2008*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	6.3	9.2	4.1
Air leak	8.5	11.1	6.6
Pulmonary hemorrhage	6.4	10.0	3.8
Severe IVH (grades III-IV)	14.0	19.0	10.4

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers*

(Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Use of High Flow (>.5L) Nasal Cannula in First 14 Days for CPAP Infants
Data as of March 27, 2008

Center	Infants born through December 2005		Infants born January 2006 to present	
	Number of infants	% of total infants	Number of infants	% of total infants
3			3	5%
4			8	19%
5			7	15%
9			12	24%
11	1	5%	6	12%
12			9	19%
13			4	17%
14	1	5%	6	8%
15			1	3%
16			3	3%
18	1	5%	7	16%
19			9	25%
22			1	6%
23			1	2%
24			1	5%
25			7	21%
Total	3	1%	85	11%

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Number
CPAP not initiated if required by protocol	3
Surfactant not given in the first hour	28
Oximeter not started within 2 hours	17
Infant placed on study oximeter for incorrect treatment	10
Failure to use study oximeter at times required by protocol	57
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	8
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	20
Other	4
Total	185

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	48
Infant placed on study oximeter for incorrect treatment	10
Failure to use study oximeter at times required by protocol	57
Non-study (unmasked) oximeter used at same time as study oximeter	7
Mechanical ventilation initiated for other than study criteria	1
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	8
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	2
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	20
Other	4
Total	185

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	1
Surfactant not given in the first hour	9
Oximeter not started within 2 hours	7
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	58

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	17
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
Infant intubated without meeting study criteria	0
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	58

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			1								1	1									3
Surfactant not given in the first hour	3	4				4	1	2	2		4		1					4	3		28
Oximeter not started within 2 hours	1	2	1			1	2			2	1	1	1			1	2	1	1		17
Infant placed on study oximeter for incorrect treatment	2		1			1	1				2		1				1		1		10
Failure to use study oximeter at times required by protocol	1	4	9		2	4	5	1	8		6		2				3	4	5	3	57
Non-study (unmasked) oximeter used at same time as study ox.						2	1			1			1						2		7
Mechanical ventilation initiated for other than study criteria																	1				1
NSIMV initiated in infant not previously intubated	1				1						4										6
Extubation (excluding unplanned) for other than study criteria						3			4		1										8
Failure to extubate CPAP infant if all criteria met								1		2											3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria			1								1										2
Infant received postnatal steroids in first 21 days of life	1					2		1	4		2	6	1				1				18
Randomization/consent errors	1	1	2		3	1				2		3	2			1	4				20
Other																					
Total	10	11	15	0	6	19	10	5	19	8	23	11	9	0	0	2	12	9	13	3	185

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – March 27, 2008

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			2%								1%	2%									0%
Surfactant not given in the first hour	5%	10%				8%	2%	8%	3%		4%		3%					20%	9%		4%
Oximeter not started within 2 hours	2%	5%	2%			2%	4%			6%	1%	2%	3%			6%	5%	5%	3%		2%
Infant placed on study oximeter for incorrect treatment	3%		2%			2%	2%				2%		3%				2%		3%		2%
Failure to use study oximeter at times required by protocol	2%	10%	20%		4%	8%	10%	4%	11%		6%		6%				7%	20%	15%	25%	7%
Non-study (unmasked) oximeter used at same time as study ox.						4%	2%			3%			3%						6%		1%
Mechanical ventilation initiated for other than study criteria																	2%				0%
NSIMV initiated in infant not previously intubated	2%				2%						4%										1%
Extubation (excluding unplanned) for other than study criteria						6%			5%		1%										1%
Failure to extubate CPAP infant if all criteria met								4%		6%											1%
Failure to extubate surfactant infant if all criteria met						2%															0%
Infant intubated without meeting study criteria			2%								1%										0%
Infant received postnatal steroids in first 21 days of life	2%					4%		4%	5%		2%	13%	3%				2%				2%
Randomization/consent errors	2%	2%	4%		6%	2%				6%		7%	6%			6%	10%				2%
Other									1%	3%	1%								3%		1%
Total protocol deviations	16%	26%	33%		12%	37%	21%	21%	26%	23%	22%	24%	25%		0%	13%	29%	45%	38%	25%	25%
Total number of infants enrolled	64	42	46	0	49	51	48	24	73	35	105	45	36	0	1	16	42	20	34	12	743

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											1										1
Surfactant not given in the first hour	4			1		2	1				1										9
Oximeter not started within 2 hours						1					5	1									7
Infant placed on study oximeter for incorrect treatment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox.															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
Infant intubated without meeting study criteria																					0
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1											1	2							4
Other											1										2
Total	7	4	0	2	0	7	1	0	4	0	17	2	1	3	3	7	0	0	0	0	58

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											3%										0%
Surfactant not given in the first hour	17%			6%		11%	10%				3%										4%
Oximeter not started within 2 hours						5%					13%	5%									2%
Infant placed on study oximeter for incorrect treatment	4%			6%							11%					2%					2%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						7%
Non-study (unmasked) oximeter used at same time as study ox.															14%						1%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
Infant intubated without meeting study criteria																					0%
Infant received postnatal steroids in first 21 days of life											3%					10%					2%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	29%	40%		12%	0%	37%	10%	0%	18%	0%	45%	11%	7%	33%	43%	17%					24%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	01	0	247

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Jan08-Mar08	Days of life 1-14	All centers	2338	38.5	7.9	76.6	15.5
		Center 16	767	37.7	8.6	80.6	10.8
	Day 15 to 36 wks	All centers	2960	33.2	12.7	71.5	15.8
		Center 16	1887	34.8	13.3	71.3	15.4
Oct07-Dec07	Days of life 1-14	All centers	11954	30.9	9.3	77.8	12.9
		Center 3	1379	34.7	8.7	77.7	13.6
		Center 5	2166	28.3	8.4	69.8	21.8
		Center 14	561	35.5	6.9	80.4	12.6
		Center 15	502	25.7	14.6	75.2	10.2
		Center 16	2717	39.7	10.5	84.4	5.2
		Center 18	1111	31.7	8.6	79.7	11.7
	Day 15 to 36 wks	All centers	45917	24.9	13.1	65.9	21.0
		Center 3	4704	30.8	14.9	69.1	15.9
		Center 5	8865	22.3	10.8	61.3	27.9
		Center 11	1141	24.6	10.2	54.2	35.6
		Center 12	1573	28.6	7.1	63.9	29.0
		Center 14	1386	20.9	13.3	63.9	22.8
		Center 15	3221	22.6	18.6	64.4	17.0
		Center 16	7385	26.1	14.8	70.6	14.5
		Center 18	1747	26.5	16.3	73.1	10.6
		Center 23	2680	28.8	10.8	61.4	27.8
		Center 25	6601	23.8	9.8	73.1	17.1
Jul07-Sep07	Days of life 1-14	All centers	14403	33.6	7.5	75.7	16.8
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1394	34.8	9.6	74.8	15.6
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 16	1162	39.8	7.4	81.8	10.7
		Center 23	2150	32.6	5.5	71.6	23.0
		Center 25	1723	39.7	5.9	83.1	11.0
	Day 15 to 36 wks	All centers	53770	24.9	11.5	65.3	23.2
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5330	22.2	9.9	59.6	30.5
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	14969	34.4	9.1	76.7	14.2
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1061	31.1	11.6	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1439	40.3	8.5	85.7	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	685	16.3	7.9	69.3	22.8
	Day 15 to 36 wks	All centers	55282	28.6	12.1	65.8	22.0
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		Center 11	4086	23.7	10.1	57.7	32.2
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	4710	29.9	13.1	69.8	17.1
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2858	22.4	9.4	55.4	35.2
Jan07-Mar07	Days of life 1-14	All centers	16812	35.4	8.3	78.1	13.6
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	54926	27.9	12.5	68.9	18.6
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
	bCenter 12	Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	[illegible]
		Center 16	3353	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	4307	20.2	17.7	64.5	17.8
Mar06-Dec06	Days of life 1-14	All centers	32802	37.2	8.2	79.0	12.9
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2419	33.1	9.1	67.5	23.4
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5667	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	881	30.5	6.0	77.5	16.6
		Center 25	1138	48.0	6.4	83.5	10.1
	Day 15 to 36 wks	All centers	107046	29.2	12.6	68.4	19.0
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3278	29.7	11.8	72.9	15.3
		Center 11	5915	29.9	10.4	61.4	28.2
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14390	29.2	12.5	69.1	18.5
		Center 18	15423	23.7	17.0	66.0	17.0
		Center 19	1281	26.6	8.0	59.8	32.3
		Center 25	6484	39.9	9.3	77.0	13.7

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH MARCH 2008

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 03/27/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Through Feb06	Days of life 1-14	All centers	27159	38.0	9.4	79.6	11.1
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1448	32.0	10.0	77.5	12.5
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1517	42.1	9.5	85.5	5.0
		Center 22	3531	40.0	8.7	79.9	11.3
	Day 15 to 36 wks	All centers	133388	26.5	12.2	67.6	20.2
		Center 3	13570	17.7	17.4	64.2	18.4
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	4802	17.3	8.5	58.1	33.4
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	{ 2	28.1	17.8	63.6	18.6
		Center 19	1919	32.8	7.0	73.3	19.8
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	3563	29.6	16.7	68.7	14.6
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

Running head: EARLY WORKING MEMORY IN INFANTS BORN ELBW

Early Working Memory and Cognition in a Cohort of Ethnically Diverse Infants Born Extremely Low Birth Weight

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INTRODUCTION:

Infants born extremely low birthweight (ELBW; <1000 grams) are at greater risk for early cognitive, attention and self-regulation difficulties (Vohr, Wright, Poole, & McDonald, 2005). These difficulties have also been shown to persist throughout childhood. Studies indicate, for instance, that children born ELBW have a higher incidence of learning difficulties, attention-deficit/ hyperactivity disorder, specific neuropsychological deficits, and behavioral problems throughout childhood (Anderson & Doyle, 2004; Hack, Friedman, & Fanaroff, 1996)

Recent research examining the role of early working memory difficulties in the cognitive, behavioral, and academic outcomes of children has highlighted the importance of working memory in outcomes of children born preterm (Woodward et al, 2005). Working memory refers to the process of holding task-relevant information in mind for brief intervals so that the information can be used to guide future actions (Goldman-Rakic, 1987) and is considered essential for higher order cognitive functioning (Bell & Wolfe, 2004). Studies examining early working memory have shown that children born preterm show impaired working memory throughout childhood (Rose and Feldman, 1996; Ross Boartright, Auld, & Nass, 1996; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Isaacs et al., 2000; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; Woodward, Edgin, Thompson, & Inder, 2005) and that impairment in this skill contributes significantly to later risks of global intellectual and academic difficulties at school in children born preterm (Rose, Feldman, & Wallace, 1992; Wolke & Meyer, 1999).

Further, there is increasing evidence that the ability to self-regulate affect and attention plays an essential role in working memory performance (Bell & Wolfe, 2004; Keenan, 2002). Previous studies have shown that infants who demonstrate self-regulatory problems have more difficulty exploring and attending to the environment, limiting their ability to engage effectively in working memory tasks (Bell & Wolfe, 2004; Keenan, 2002). Although the association between self-regulation and working memory performance has been demonstrated in infants born full-term (Bell & Wolfe, 2004; Keenan, 2002), no study to date has examined this relationship in a population of extremely preterm infants.

The purpose of this study was to better understand early working memory as measured by object permanence tasks in 18 – 22 month olds born ELBW, compared to measures of cognition and self-regulation (i.e., emotional and attentional regulation). We hypothesized that children with lower birthweights and higher illness severity would have more difficulty on the object permanence tasks. In addition we hypothesized that working memory problems would be directly related to difficulty in emotional and attention regulation. The impact of ethnicity, gender, illness severity, and family socio-economic status on object permanence performance was also examined. Object permanence performance was not expected to differ by ethnicity, given that these tasks should be culturally neutral.

METHODS

Population and study protocol

Infants eligible for this follow-up study were surviving infants who had been enrolled in a multicenter study of low-dose hydrocortisone therapy for prophylaxis of

early adrenal insufficiency. Singletons and twins between 500 and 999 grams birth weight were eligible if they were mechanically ventilated at study entry (12 - 48 hours postnatal age). The study protocol was approved by institutional review boards at all participating institutions and parental consent was obtained prior to enrollment. At the evaluation, demographic and medical histories were obtained. Weight, height and head circumference were recorded.

Development was assessed with the Bayley Scales of Infant Development II (BSID-II; 13) with a Mental Developmental Index (MDI) calculated as a measure of cognition. Emotional regulation and attentional regulation were assessed using the Emotional Regulation and Orientation/Engagement scales of the BSID-II Behavior Rating Scale, respectively. Items 84, 96, and 102 of the BSID-II Mental Scale were used as measures of object permanence. Children were asked to find a toy hidden under one of two cups with double visual displacement utilized (the toy was hidden under one cup, removed and hidden a second time under the second cup) to increase the difficulty of the item. The number of object permanence items correctly completed was calculated for each child. This number was dichotomized, grouping those who correctly completed 0 or 1 items **or those who correctly completed 2 or 3 items (which included the item with double visual displacement). Object permanence mastery was defined as correctly completing 2 or 3 items.** The Clinical Risk Index for Babies (CRIB) score, birthweight, and gestational age were used to examine medical illness severity, while household income and maternal education were used as family socio-economic variables. All examiners administering the BSID-II were trained and certified.

Statistical analysis

Neurodevelopmental outcomes were analyzed using analysis of covariance for continuous outcomes and logistic regression for binary outcomes. These analyses included adjustment for the stratification variable birth weight (continuous form) and the following baseline characteristics: gestational age, CRIB score, gender, ethnicity, maternal education and household income. Hydrocortisone treatment was not included as a variable in these analyses. For analysis of ethnic group, six children (4 Native American, 2 Black Hispanics) were omitted, as there were insufficient numbers to adequately study these groups and to avoid arbitrary pooling. Unless otherwise noted, all hypotheses tests were two-sided and used a significance level of 0.05. All statistical analyses were conducted using SAS Version 9 (SAS Institute Inc., Cary, NC). Family demographic characteristics at follow up are shown in Table 1 with children grouped by ethnicity/race.

RESULTS:

A significant relationship was found between object permanence and cognition (BSID-II MDI), such that, MDI scores increased as did the odds of object permanence mastery ($p<0.0001$). When adjusted for CRIB score, both MDI ($p<0.0001$) and CRIB ($p=0.04$) were significant. Object permanence mastery also had significant positive relationships with orientation/engagement (measure of attention) and emotional regulation scores (measure of self-regulation) on the Behavior Record of the Bayley Scales ($p<0.0001$ and $p=0.0004$ respectively). The relationship between object permanence mastery and Orientation/ Engagement as well as between object permanence mastery and Emotional Regulation remained significant after controlling for medical illness severity variables and socio-economic variables.

Girls performed significantly better than boys on object permanence tasks (p=0.002). When maternal education and household income were included as covariates, gender remained significant (p=0.0004). Neither socio-economic nor medical illness severity variables were significantly related to object permanence mastery.

No significant differences were found between ethnic groups in object permanence mastery; however, there was a significant effect of ethnic group on MDI score, such that Hispanic, Asians and African American infants had significantly lower MDI scores than Caucasian children (see Table 2). These differences remained significant after controlling for medical illness severity and socio-economic variables. A significant difference was also found on a measure of attentional regulation (BSID-II Orientation/Engagement), with Black children performing less well than Caucasian children (see Table 2).This difference could not be accounted for by socio-economic or medical illness severity variables. No ethnic differences were found on emotional regulation (BSID-II Emotional Regulation).

Ethnicity	MDI		Orientation Engagement	
	Mean ± SD	p-value*	Mean ± SD	p-value*
Caucasian (n=118)	85.90 ± 19.96		47.38 ± 28.09	
Black (n=90)	72.48 ± 15.95	<0.0001	38.29 ± 23.47	0.0156
Hispanic (n=25)	77.38 ± 16.52	0.04	45.24 ± 27.93	0.71
Asian (n=11)	69.27 ± 19.86	0.004	37.45 ± 24.49	0.23

* p-value for comparison to Caucasian group, including adjustment for the stratification variable birth weight (continuous form) and the following baseline characteristics: gestational age, CRIB score, gender, ethnicity, maternal education and household income.

DISCUSSION:

The primary purpose of this study was to better understand early working memory in 18 – 22 month olds born ELBW by examining the association between object permanence and self regulation (i.e., emotional and attentional regulation) as well as the impact of ethnicity, gender, illness severity, and family socio-economic status on object permanence performance. We found that object permanence mastery was highly correlated with measures of self-regulation, indicating that emotional and attention regulation difficulties in children born ELBW are associated with poorer performance on measures of early working memory such as object permanence tasks. In addition we found a significant gender difference in object permanence mastery, with girls having twice the likelihood of achieving higher levels of object permanence than boys. Contrary to our expectations, medical illness severity and family socio-economic variables were not significantly associated with object permanence mastery. As we hypothesized, object permanence performance was not impacted by ethnicity or race, in contrast to MDI scores, which were significantly affected by race and ethnic group.

Piaget first identified different types of early problem solving skills that were developmental in nature when he wrote about sensori-motor and concrete operational skills in toddlers (Piaget, 1953). Using his theory, tasks were created to measure early reasoning skills in preschoolers that were associated with prefrontal cortex cognitive deficits such as the A not B test (Diamond, 1997). Similar tasks of object permanence are imbedded within traditional tests of infant intelligence, such as the Bayley Scales of Infant Development (1985), though these tasks have not been studied separately as a

measure of working memory, at 18-22 months in children born ELBW. Recently several studies have examined at working memory as a measure of executive functioning in school age outcome studies for children born preterm (Curtis et al, 2002; Luciana, Lindeke, & Georgieff, 1999). Woodward et al (2005) found that two year old children born preterm compared to those born at term, had difficulty encoding new information in working memory. On MRI scan, children born preterm had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parietooccipital and premotor areas). Expanding such research to infants and younger children would be beneficial, as it has been well documented that the Bayley Scales of Infant Development, frequently used as an outcome measure for neonatal studies, is a poor predictor of later cognitive function (Hack et al, 2005).

As defined by Goldman-Rakic (1987) working memory is a process that involves holding task relevant information in mind for brief intervals so that the information can be used to guide future actions. Interconnections between the frontal cortex, caudate nucleus and hippocampus have been found to be integral for working-memory function (Alexander et al, 1986; Goldman-Rakic, 1987). Researchers have been trying to better understand factors related to school failure and success, in children born preterm (Nelson et al, 2002; Luciana, et al. 1999) Studies looking at working memory, executive function and CNS imaging in infants and toddlers born ELBW may help link functional and structural knowledge of specific learning and self-regulatory problems that develop with infants born preterm. Aylward (2005) summarized that 'executive function deficits may be subtle, though they could have substantial impact on cognitive, social and academic functioning' (pg. 434). In addition, deficits in skills related to executive function have

been found to affect attention and self-regulation; for example ADHD has been found to occur 2.6 to 4 times more frequently in children born very low or extremely low birth weight (Whitaker, Van Rosen and Feldman, 1997), 60 to 70% of ELBW children have been reported to require special assistance in school (Saigal, den Ouden, & Wolke, 2003). Early identification of learning and self-regulatory differences in this population may permit utilization of early intervention techniques to ameliorate these school-age problems.

The effect of gender on tests of working memory has not been reported; however, gender has been found to affect (Luciana, 1999; Anderson et al, 2004) measures of cognition in 18-22 month olds born both VLBW and ELBW (Hoekstra et al, 2004; Hintz et al, 2006). For example Hack et al (2000) found that male gender was a significant predictor of a subnormal MDI score with an odds ratio of 2.73. In addition a study of school age children found that 11 year old boys born preterm at had a three to six fold increase in learning disorders compared to controls (Johnson et al, 2000). Such differences have also been noted in young children born VLBW, though Luciana (1999) proposed that NICU survivors have a developmental delay in brain maturation, which could be greater in boys as indicated by our findings.

The impact of ethnicity on intelligence testing has been explored since the 1960's when Arthur Jensen began the scholarly debate on race and intelligence. Outcome studies have been mixed with some indicating that maternal race added prognostic information to poorer developmental outcome (Schmidt et al 2003), though others attributed differences to socioeconomic status (Lowe et al, 2005), maternal education (Laptook et al, 2005) or nonwhite race (Hoekstra, et al, 2004, Vohr, 2005). Findings regarding differences in

specifically nonwhite race groups were mainly on tests of intelligence such as the Wechsler Preschool and Primary Scale of Intelligence-Third (WIPPSI-III) (Wechsler,2002) or the Bayley Scales of Infant Development. Our findings that the working memory items from the Bayley Scales of Infant Development II were not different between ethnic groups, while the MDI score was, provides an additional reason to explore measures of working memory and other executive function as more ethnically unbiased in contrast to tests of cognition.

Limitation of our study include the lack of a term control group and the small numbers within our ethnic groups, especially Hispanics and Asians. In addition, the items of object permanence were taken from the Bayley Scales of Infant Development and did not have the increasing delays required to find an item, that the A not B task requires. These items were also part of the overall MDI score, though they only represented 3 of over 25 items generally administered.

Further studies examining ways to better assess working memory in children born ELBW at young ages, including the first year of life, could assist in better identification of those children at greater risk for later attention and learning problems. Measures of working memory should be included in future studies that measure developmental outcome, allowing us to go beyond measures of cognition which can be ethnically biased. Research expanded to better understand brain-behavior relationships of early pre-frontal skills in this vulnerable population could improve our ability to intervene earlier when working with children born ELBW.

NICHD HD38540.

CRIB REFERENCE: The International Neonatal Network. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet* 1993;342 : 193-98

Date: November 30, 2007

To: Neonatal Research Network Follow-up Committee, Betty Vohr, Chair

From: Jean Lowe Ph.D. and Janell Fuller, MD
University of New Mexico

Re: Proposal for ancillary study to the SUPPORT trial, "Evaluation of early working memory in extremely preterm infants"

Synopsis: We propose to study early working memory in extremely preterm infants enrolled in the NICHD SUPPORT trial by recording and analyzing responses to 3 specific items from the Bayley Scales of Infant Development-III (2006) (Bayley-III), which measure object permanence (items 40, 45 and 50), and evaluating the relationship of "mastery of object permanence" to performance on the Bayley-III at 18 – 22 months, to MRI findings at term gestation, and to performance on tests of executive function at 6 – 7 years of age.

Our specific **hypotheses** are that:

- infants born extremely preterm (<28 0/7 weeks) who achieve object permanence mastery will do significantly better on the Bayley-III test of Cognition and Language at 18-22 months than those who do not.
- in contrast to Bayley Cognitive and Language scores, object permanence mastery at 18 months will **not** be affected by SES or ethnic grouping.
- children who achieve object permanence mastery will have significantly **fewer** abnormal findings on the MRI performed at term as part of the SUPPORT trial.

- children who obtain object permanence mastery will perform significantly better on tests of executive function at 6 and 7 years.

Background and significance:

Research related to Executive Function: Executive function is an umbrella term that encompasses three main areas: working memory, inhibition and cognitive flexibility (Davidson, Amso, Anderson & Diamond, 2005). Recently we have seen more studies that look at working memory as a measure of executive functioning in school age outcome studies (Anderson, et al, 2004; Curtis et al, 2002; Luciana, Lindeke, & Georgieff, 1999) with significant differences found between executive functioning in those children born preterm in comparison to children born at term. Studies have shown executive function deficits in children school-aged and older who were born prematurely (Anderson, & Doyle, 2004), which persist even after taking IQ differences into account (Bayless & Stevenson, 2007).

In one of the few studies of executive function with young children born preterm Woodward et al (2005) found that 2 year olds born preterm in comparison to those born at term, had difficulty encoding new information in working memory, and on MRI children born preterm had bilateral reduction in cerebral tissue volume in areas specifically related to working memory (dorsolateral prefrontal cortex, parietooccipital and premotor areas). Studying these vulnerable populations at younger ages could result in executive function interventions that could be clinically useful. New measures have recently been developed which allow researchers to tap into the foundations of executive function in very young children, particularly their working memory, impulse control, and

rule use (Carlson, 2005). Although these new measures for preschool children have been employed with typically developing populations (Carlson, 2005) there are currently very few studies investigating executive function in preschool children born prematurely. The few studies that have been conducted found that preschoolers born VLBW without major neurological deficits may have specific difficulty in sustained attention, visuospatial processing, and spatial working memory when compared with full term children matched for chronological age and IQ (Vicari, Caravale, & Carlesimo, 2004).

A recent randomized trial of early hydrocortisone treatment (Watterberg et al, 2007) found that fewer hydrocortisone-treated patients had a Bayley-II MDI of <70 and that more of the hydrocortisone-treated children showed evidence of awareness of object permanence on the Bayley-II. Further investigation indicated that MDI scores were significantly higher in the white ethnic group while object permanence mastery was relatively similar across all ethnic groups (Blacks, Hispanics, Asians, whites). (Lowe et al, manuscript in preparation and attached).

Our finding that object permanence mastery is not impacted by either ethnic group or income is relevant to how we could improve our way of identifying those children 'at-risk' for later developmental sequelae, as the Bayley Scales MDI, frequently used in research as an outcome measure, is a poor predictor of later cognitive function (Hack et al, 2005). Object permanence items as a measure of early working memory (Diamond, et al. 1997) have been related to the development of prefrontal cortical function (Woodward, et al.2005) and the earliest measure of reasoning skills in toddlers. This is relevant to intervention techniques that can be developed to specifically work on tasks that could enhance these skills. In conjunction with the Bayley Scales cognitive

score, use of a measure of object permanence may also improve our detection of ongoing problems with executive function at 18-22 months, which is highly related to later learning difficulties.

Study design: We propose to separately record items 40, 45 and 50 from the Bayley-III Cognitive Scale in infants enrolled in the SUPPORT trial, and to analyze the relationship of 'mastery of object permanence', defined as achievement of two of these items, to (1) MRI findings at term gestation (done for the imaging secondary of the SUPPORT trial; (2) Bayley-III Cognitive scale and factors affecting performance on both the cognitive scale and object permanence achievement; and (3) tests of executive function at 6 and 7 years within the proposed long-term follow up study of infants enrolled in the SUPPORT trial.

This ancillary study cannot be deferred until the long-term follow up study for SUPPORT is either approved or disapproved, because children in the SUPPORT trial are beginning to enter the 18 – 22 month window. This study would be easy to add on, as it would only require extracting results from the Bayley-III Cognitive Scale and recording them for data collection. If the 6 – 7 year follow up is not approved, collecting these data will still be valuable in assessing the relationship of mastery of object permanence to MRI findings and to Bayley performance in a large cohort of extremely preterm infants.

Budget: The budget would only require (1) a minimal increase in data collection and entry time and (2) statistical analysis. Bayley examiners can fill in the coding sheet noting specific performance on these items at the time the test is performed and scored. No additional testing, equipment or training is required.

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From: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Das, Abhik; Suzy Ventura; Abbot Laptook; Betty Vohr
Subject: RE: SUPPORT
Date: Friday, March 28, 2008 9:36:27 AM

Please see responses below.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 27, 2008 3:23 PM
To: Abbot Laptook; Betty Vohr; Angelita Hensman
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,
Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.
This is outstanding given your recruitment!!! Keep up the great work!
Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. No further appointments to be scheduled. Info was entered on 03/11/08. However there was a data entry error. Final Acute Status- Lost to Follow up at 55 weeks PMA was entered as 'N'. This should be 'Y'.
14	(b) (6)	The DMS was updated today and RTI should receive the correction with the next transmission.
14	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	BPD_message
14	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered) PHY01 form was not needed. No option to delete it at our end. To be deleted by RTI today.
14	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered) PHY01 form was not needed.To be deleted by RTI today.
CENTER	NETWORK	FU_message
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed - tracking ongoing -mom previously in a shelter in CT
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed - Same as above.(Twins)
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed - tracking ongoing
14	(b) (6)	FU window has closed but NF05 and NF09a have not been completed - tracking ongoing
14	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed - Form has been completed and will be entered.

Rosemary D. Higgins, MD
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich; Elaine Romano
Subject: Re: SUPPORT
Date: Thursday, March 27, 2008 4:42:25 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> HI,
> Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.
>
> Thanks for all the effort!!!
> Rose
>
> | CENTER | NETWORK | ROP_message |
> |---|---|---|
> | 13 | (b) (6) | 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
> | 13 | (b) (6) | 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
>
> Rosemary D. Higgins, MD
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
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> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Funny you should send this reminder today, do you want the good news or the bad news first?
Baby (b) (6) I had an eye appointment today at our eye clinic (rescheduled after being a no show ealier this month) and the baby had her eyes dilated but then the parents left before she was examined because they had to go to work!! Elaine Romano will try and call them next week but I am not going to make any promises. The second baby had an eye exam with an opthamologist not from our site so we are trying to work it out to get the results for his final eye exam.
Monica

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Monica Collins; Myriam Peralta, M.D.; scrosby@peds.uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT
Date: Thursday, March 27, 2008 4:28:31 PM

Final ROP exam status has been entered today on ID (b) (6) and we're currently working on rescheduling (b) (6) for the 18 month follow up visit – patient has missed **2 appts.**
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 27, 2008 2:28 PM
To: wacarlo@uab.edu; Monica Collins; Myriam Peralta, M.D.; Vivien Phillips; scrosby@peds.uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,
Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.
This is amazing given your phenomenonal recruitment!!!
Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

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

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Monica Collins; Myriam Peralta, M.D.; Vivien Phillips; scrosby@peds.uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT
Date: Thursday, March 27, 2008 4:25:05 PM

Rose:

Thanks. Our nurses are doing an exceptional job! They always do☺

We will get the data. Thanks identify these.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 27, 2008 2:28 PM
To: wacarlo@uab.edu; Monica Collins; Myriam Peralta, M.D.; Vivien Phillips; scrosby@peds.uab.edu
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

HI,
Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.
This is amazing given your phenomenonal recruitment!!!
Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
16	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
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From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Thursday, March 27, 2008 3:57:42 PM

I have this data and jsut need to get it entered.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 03/27/08 2:15 PM >>>
HI,

Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

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higginsr@mail.nih.gov

From: Katherine A Foy
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Michael Cotten; Ronald N Goldberg; Ricki F Goldstein; lohme001@mc.duke.edu; Gantz, Marie
Subject: Re: SUPPORT
Date: Thursday, March 27, 2008 3:48:32 PM

I have almost completed the list. I have two more to do and I will be done.
Have a great day,

Kathy Foy
Clinical Research Coordinator
Duke University Health Systems
Neonatology
668-3360 office
970(b) (6) pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 03/27/2008 03:40 PM

To: "Ronald N Goldberg" <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Katherine A Foy" <foy00004@mc.duke.edu>, <lohme001@mc.duke.edu>

cc: "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>

Subject: SUPPORT

HI,
Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER NETWORK ROP_message

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.

CENTER NETWORK BPD_message

19 (b) (6) PHY01 is expected based on NG07 but has not been entered

19 (b) (6) Infant was hospitalized at 36 weeks (per NG03) but NG07 36 week snapshot is missing

CENTER NETWORK FU_message

19 (b) (6) FU marked as complete (per NF10/SF10) but NF09a has not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD
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From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Janet Morgan; Melissa Leps; Pablo Sanchez; Roy Heyne
Cc: Abhik Das; Marie Gantz
Subject: Re: SUPPORT
Date: Thursday, March 27, 2008 3:45:50 PM

I keyed the last ROP exam for (b) (6) into the computer on 3/10/08. Results showed "fully vascularized" I may not have transmitted until 3/25/08.
Thanks,
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 3/27/2008 2:15 PM >>>
HI,

Here is a list of missing SUPPORT outcomes as of the March 18 data download. Let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Finer, Neil; Rich, Wade; Pickett, James; Auman, Jeanette O.
Subject: Malfunctioning Support oximeters
Date: Wednesday, March 26, 2008 11:48:51 AM
Importance: High

Hi all,
Please see below. Utah sent New Mexico 4 orange oximeters this morning. Julie is sending me a list of the malfunctioning oximeter serial numbers and I will call Marybeth Sayre to see if we can have them replaced asap. It seems only the orange oximeters are malfunctioning but it happens that the last couple of randomizations have all been orange so Julie is not sure if the blue coded oximeters will malfunction as well.

Marie and James, I've asked Julie to send the Network number of the infant case below just so it is noted.
Thanks,
Kris

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Wednesday, March 26, 2008 11:26 AM
To: Zaterka-Baxter, Kristin
Subject: RE: ORANGE OXIMETERS PLEASE

Well, as it is the best we can do, what else can we do?
Sadly, for our patient on the study we had major issues with the oximeters yesterday.
All 3 of the available orange oximeters (the other 2 are still in clinical engineering) were tried on our patient yesterday and all 3 were malfunctioning. The sat values on the Masimo screens were jumping all over the place (erratically) and were at times were a value 25 below the Nellcor (which we had to have on for safety as we knew the Masimos were malfunctioning). This is a very sick baby on an oscillator and we must have accurate sat readings. Also, if the nurses were to increase FiO2 based on the inaccurate Masimo values then we could cause harm to the baby. (not to mention the fact that the Masimos were alarming constantly) So Dr. Watterberg made the decision for patient safety that until we can get in a correctly functioning Masimo we remove the study oximeter. So we will lose some data. But as I told you, I really question the validity of the data when the machines are clearly not giving an accurate value.
Thanks for your help.
Julie

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 3/26/2008 7:02 AM >>>
Hi Julie, just to be sure you received a message about the oximeters, Karen is going to send the oximeters to you this am to you so that you will receive them by Thursday. They could not get them out yesterday, hope this will be ok?
Thanks,
Kris

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Tuesday, March 25, 2008 6:17 PM
To: Karen Osborne RN; Zaterka-Baxter, Kristin
Subject: Re: ORANGE OXIMETERS PLEASE

Can I please add a little to the sending address to make sure that they get to me.
University of New Mexico
Department of Pediatrics/Neonatology
Attn: Julie Rohr/Anne Debuyserie
915 Camino de Salud NE
Albuquerque NM 87131
JRohr@salud.unm.edu
505-272-0363

We really appreciate the help.
Juli
Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

e
>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 3/25/2008 3:08 PM >>>
HI Karen,
I left you a voicemail just a few minutes ago; by any chance do you still have a few extra orange oximeters you could send to New Mexico this evening? They need about 4 but any spares you have would be great. The address is below. Please call my cell if you have any questions.
Much appreciated.
Kris

Julie Rohr
Department of Pediatrics
915 Camino de Salud NE
Albuquerque NM 87131
JRohr@salud.unm.edu
505-272-0363

Kris Zaterka-Baxter
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(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
4426 South Miami Blvd

Durham, NC 27703 USA

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT SAE
Date: Tuesday, March 25, 2008 2:04:35 PM

Dear Rose,

I do not know if you remember or not about a sad little baby we had in the SUPPORT study that we thought would die before Christmas--but then he never did. This little child was transferred to our children's hospital the first of this month for a pulmonary consult and we have just today found out the he passed away(b) (6) . I need a few more details and will send the SAE for the death--not related to study. Child was born(b) (6)

Ellen

Ellen Hale, RN, BS

Research Nurse Coordinator
Neonatal Research Network
Emory University School of Medicine

Office 404-616-4218
Fax 404-524-3953

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY
Date: Saturday, March 22, 2008 12:13:49 PM

I agree it is simple and could be added. I would suggest that the FU people make sure it is feasible to add this memory testing to the 6-7 year appt.

Sorry for the delayed response. I did not have good email access during the 2 week(b) (6)

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 11, 2008 8:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY

HI,
I have yet to receive feedback on this ancillary study –we have a SUPPORT call scheduled for April 1 at 3 PM and I will add it to the agenda.

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 23, 2008 3:34 PM
To: nfiner@ucsd.edu; 'Walsh, Michele'; wacarlo@uab.edu; 'wrich@ucsd.edu'; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; 'Abbot Laptook'; kurt.schibler@cchmc.org; 'nancy newman'; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Newman, Jamie; 'Susan Hintz'
Subject: SUPPORT ANCILLARY STUDY

Hi
Attached is a secondary to SUPPORT for FU and potential 6-7 year FU. Let me know if you would like to have a call to discuss. I have included Susan Hintz on the email as this relates to the MRI/FU and the

potential 6-7 year FU protocol.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing Outcomes
Date: Wednesday, March 19, 2008 11:50:16 AM
Attachments: Infants with missing outcomes 03-19-08.xls

Rose,

Attached is the list of infants with missing outcomes for this month.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
15		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
15		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.
22		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
25		Infant died at approximately 44 weeks PMA, and no ROP exams have been entered. Please enter any exams or confirm that no ROP exams were done.

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter
Subject: Re: SUPPORT MedWatch
Date: Tuesday, March 18, 2008 10:36:51 AM

Rose and Kris,
We had a death in the SUPPORT study(b) (6) . The NN# will be(b) (6) It was not related to the study. The baby lived just over 24 hours, developed acidosis, pulmonary hemorrhage, was coded X 2 and didn't respond. MedWatch is pending.
I also have an AE on another SUPPORT baby for PIE since birth and a Grade III IVH.
NN# is(b) (6).
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From:	Finer, Neil
To:	Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; wacarlo@uab.edu; Rich, Wade; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject:	RE: SUPPORT ANCILLARY STUDY
Date:	Sunday, March 16, 2008 2:38:21 PM

I think we can have a good discussion about this protocol during our next call
Thanks to everyone who has responded
Neil

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Sunday, March 16, 2008 8:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Walsh, Michele; wacarlo@uab.edu; Rich, Wade; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY

Rose
I think this study is very reasonable and a good use of the data. It would appear to be feasible with or without the 6-7 yr follow-up but would be stronger with the later follow-up. Shouldn't this proposal include a little more of the specifics regarding what aspects of the MRI will be analyzed, sample size needed, analytical plan including covariates. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 11, 2008 9:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY

HI,
I have yet to receive feedback on this ancillary study –we have a SUPPORT call scheduled for April 1 at 3 PM and I will add it to the agenda.

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 23, 2008 3:34 PM
To: nfiner@ucsd.edu; 'Walsh, Michele'; wacarlo@uab.edu; 'wrich@ucsd.edu'; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; 'Abbot Laptook'; kurt.schibler@cchmc.org; 'nancy newman'; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Newman, Jamie; 'Susan Hintz'
Subject: SUPPORT ANCILLARY STUDY

Hi
Attached is a secondary to SUPPORT for FU and potential 6-7 year FU. Let me know if you would like to

have a call to discuss. I have included Susan Hintz on the email as this relates to the MRI/FU and the potential 6-7 year FU protocol.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Walsh, Michele
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Rich, Wade; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org; Rich, Wade
Subject: RE: SUPPORT ANCILLARY STUDY
Date: Friday, March 14, 2008 10:02:03 AM

I responded previously that I did not believe that there was sufficient time to institute within the construct of the current trial. SUPPORT has a lot of well conceived secondaries, I am not in favor of adding more at this late date. This could be done within Inositol.

Michele Walsh
phone: 216-844-3759

From: Finer, Neil [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Thursday, March 13, 2008 7:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; wacarlo@uab.edu; Rich, Wade; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org; Rich, Wade
Subject: RE: SUPPORT ANCILLARY STUDY

Hi Rose
I think that a discussion of this proposal would be good. Has there been any agreement to extend the SUPPORT follow-up??
It would appear that if the follow-up period is extended, that this study would be relatively easily accommodated. This is labeled an Ancillary – is it proposed for only one or centers?
I look forward to the input of others.
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 11, 2008 6:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Walsh, Michele; wacarlo@uab.edu; Rich, Wade; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY

HI,
I have yet to receive feedback on this ancillary study –we have a SUPPORT call scheduled for April 1 at 3 PM and I will add it to the agenda.

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 23, 2008 3:34 PM
To: nfiner@ucsd.edu; 'Walsh, Michele'; wacarlo@uab.edu; 'wrich@ucsd.edu'; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; 'Abbot Laptook'; kurt.schibler@cchmc.org; 'nancy newman';

Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Newman, Jamie; 'Susan Hintz'
Subject: SUPPORT ANCILLARY STUDY

Hi
Attached is a secondary to SUPPORT for FU and potential 6-7 year FU. Let me know if you would like to have a call to discuss. I have included Susan Hintz on the email as this relates to the MRI/FU and the potential 6-7 year FU protocol.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: nancy newman
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ANCILLARY STUDY
Date: Wednesday, March 12, 2008 1:44:24 PM

Hi Rose- the ancillary study proposed seems to be something that would fit in without extra resources and if long term f/u is approved as well it would work as I assume testing at 6-7 y would include executive functioning or could easily be included- but I am not familiar with tests that would be used. Not sure this helps.....Nancy

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 11, 2008 9:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz; petrie@rti.org
Subject: RE: SUPPORT ANCILLARY STUDY

HI,
I have yet to receive feedback on this ancillary study –we have a SUPPORT call scheduled for April 1 at 3 PM and I will add it to the agenda.

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 23, 2008 3:34 PM
To: nfiner@ucsd.edu; 'Walsh, Michele'; wacarlo@uab.edu; 'wrich@ucsd.edu'; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; 'Abbot Laptook'; kurt.schibler@cchmc.org; 'nancy newman'; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Newman, Jamie; 'Susan Hintz'
Subject: SUPPORT ANCILLARY STUDY

Hi
Attached is a secondary to SUPPORT for FU and potential 6-7 year FU. Let me know if you would like to have a call to discuss. I have included Susan Hintz on the email as this relates to the MRI/FU and the potential 6-7 year FU protocol.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NeOProM collaboration
Date: Thursday, March 06, 2008 4:10:55 PM

I agree

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, March 06, 2008 12:47 PM
To: Finer, Neil
Subject: FW: NeOProM collaboration

Neil
See the request below – we can discuss this on the subcommittee call.

I think these are reasonable items:
Can you please tell me when your recruitment commenced, how many babies have been recruited, if you are meeting your targets for recruitment, what is your estimated finishing date and what % of parents approached consent for the trial.

We are also interested in oxygenation compliance from each trial. Can you tell me how you are measuring compliance - ie how often on how many babies etc

I will find out if our DSMC is "public knowledge."

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, February 22, 2008 4:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NeOProM collaboration

Hi,
Has the SC had a chance to weigh in about giving out the info below or are they planning on discussing it during the Support call prior to the April SCM?
Thanks,
Kris

From: Charlene Thornton [mailto:cthornton@ctc.usyd.edu.au]
Sent: Sunday, February 10, 2008 5:26 PM

To: Zaterka-Baxter, Kristin
Subject: NeOProM collaboration

Dear Kris

I was forwarded your name by Rose Higgins as the Lead Co-ordinator for the SUPPORT trial.

I am the co-ordinator for the prospective meta-analysis being conducted on all of the oxygenation trials (NeOProM) of which SUPPORT is a collaborator.

I am organising a meeting of all collaborators as a satellite meeting at the PAS conference in May in Hawaii. I will include you on all emails concerning this meeting.

We have a copy of your protocol for SUPPORT but I require some information prior to arranging the meeting.

In order to maximise the topics which can be covered in the meeting, I want to have a written update of where recruitment is up to for all of the trials.

Can you please tell me when your recruitment commenced, how many babies have been recruited, if you are meeting your targets for recruitment, what is your estimated finishing date and what % of parents approached consent for the trial.

We are also interested in oxygenation compliance from each trial. Can you tell me how you are measuring compliance - ie how often on how many babies etc

The final issue is your data safety monitoring committee. Are you able to tell me the names of the members and how often they meet.

Sorry for all of the questions - but we are keen to formalise this PMA and make the collaboration as successful as possible.

Kind regards

Charlene Thornton
Systematic Reviews Officer
University of Sydney
NHMRC Clinical Trials Centre

From: Betty Vohr
To: Newman, Jamie; JANET.MORGAN@childrens.com
Cc: Roy.Heyne@UTSouthwestern.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT patient with Bayley II rather than III - Ctr 4 Dallas
Date: Monday, March 03, 2008 1:46:24 PM

Probably correct. Although, we do not know if the MDI was impacted by low language skills.

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, March 03, 2008 1:29 PM
To: JANET.MORGAN@childrens.com
Cc: Roy.Heyne@UTSouthwestern.edu; Betty Vohr; higginsr@mail.nih.gov; Das, Abhik
Subject: SUPPORT patient with Bayley II rather than III - Ctr 4 Dallas

Janet,
Though it would be "nice" to have a Bayley III on the SUPPORT patient below, this infant would classify as impaired for analysis purposes.

Center ID Number	Network Number	Ctr Random	Follow Up Number	Follow Up Date	Bayley II Date	Bayley II Adjusted Age	MDI	PDI	Bayley III Date	Bayley III Adjusted Age	Bayley III Composite Cognitive Score
4	(b) (6)	4	(b) (6)	(b) (6)	01/25/08	24	58	73	.	.	.

Thanks again for bringing this patient to our attention.
Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Newman, Jamie
To: adusick@iupui.edu; ldrichar@iupui.edu
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; BVohr@WIHRI.org
Subject: SUPPORT patient with Bayley 2 rather than 3 - Ctr 12 Indiana
Date: Monday, March 03, 2008 1:26:34 PM

Our records show that there is a SUPPORT patient at your center that has a Bayley II and not a Bayley III at follow-up.

Center ID Number	Network Number	FU Center	Follow-Up Number	Delivery Date	Bayley FU Date	Bayley Adjusted Age	MDI	PDI	Bayley III Date	Bayley III Adj Age	Bayley III Composite
12	(b) (6)	12	(b) (6)		03/07/07	19	50	50	.	.	.

Though it would be "nice" to have a Bayley III on this patient, this infant would classify as impaired for analysis purposes. Please note that all SUPPORT patients seen at follow-up should have a Bayley III (3) as is specified in Technical Memo #31 (dated 2/1/07). Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Zaterka-Baxter, Kristin
To: Susan Hintz; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.
Subject: RE: first 100 SUPPORT neuroimaging secondary patients
Date: Thursday, February 28, 2008 2:08:38 PM
Attachments: First100BrainMRIs.xls

Hi Susan,
Please take a look at this spreadsheet and let me know if this is what you are looking for.
Thanks much,
Kris

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, February 27, 2008 6:33 PM
To: Das, Abhik
Cc: Zaterka-Baxter, Kristin; higginsr@mail.nih.gov
Subject: first 100 SUPPORT neuroimaging secondary patients

Hi Abhik and Kris,

I am working on the revision of the 6-7 year follow-up of SUPPORT Neuroimaging proposal, and I need some information. Rose and Jane Hammond and I were discussing the very long window for the 6-7 year follow-up (i.e., if the first patient birth date was May 2005, and the last will be in early 2009, then the window would span May 2011 to early 2016). But we are all aware of the stop-restart during the SUPPORT trial, and also I believe that enrollment in the Neuroimaging secondary was pretty slow in the beginning because many centers had not gotten IRB approval before the stop-restart, and then we had the next cycle and new centers joined. SO - it would help me greatly if I could have a spreadsheet of the FIRST 100 patients (listed by birth date) in the SUPPORT neuroimaging secondary (i.e., that actually got the MRI). At least then I could see how the stops/starts/glitches play out in terms of how few or many patients will be in the beginning of that very long window -

Attached is a little mock spreadsheet -

If at all possible, could I have it tomorrow or Friday?

thanks

Susan

Birth Date	CENTER	NETWORK	Enrolled in MRI Secondary	Successful Brain MRI	MRI
(b) (6)	15	(b) (6)	Y	Y	07/01/2005
	15		Y	Y	08/01/2005
	22		Y	Y	10/26/2005
	22		Y	Y	10/26/2005
	22		Y	Y	11/03/2005
	22		Y	Y	11/17/2005
	22		Y	Y	11/15/2005
	22		Y	Y	11/15/2005
	22		Y	Y	11/21/2005
	22		Y	Y	02/09/2006
	21		Y	Y	06/13/2006
	03		Y	Y	06/27/2006
	03		Y	Y	06/30/2006
	03		Y	Y	06/23/2006
	14		Y	Y	06/23/2006
	14		Y	Y	06/23/2006
	03		Y	Y	06/14/2006
	18		Y	Y	06/06/2006
	18		Y	Y	07/08/2006
	18		Y	Y	07/08/2006
	18		Y	Y	06/23/2006
	03		Y	Y	08/21/2006
	04		Y	Y	07/10/2006
	15		Y	Y	07/19/2006
	15		Y	Y	07/11/2006
	18		Y	Y	07/26/2006
	14		Y	Y	07/11/2006
	03		Y	Y	07/27/2006
	03		Y	Y	08/17/2006
	18		Y	Y	08/23/2006
	16		Y	Y	08/22/2006
	16		Y	Y	09/01/2006
	03		Y	Y	08/14/2006
	14		Y	Y	08/30/2006
	14		Y	Y	09/14/2006
	04		Y	Y	08/23/2006
	04		Y	Y	08/22/2006
	04		Y	Y	09/18/2006
	18		Y	Y	08/21/2006
	14		Y	Y	09/15/2006
	16		Y	Y	10/11/2006
	16		Y	Y	09/05/2006
	16		Y	Y	09/22/2006
	16		Y	Y	09/22/2006
	19		Y	Y	11/07/2006
	15		Y	Y	08/31/2006
	14		Y	Y	09/20/2006
	16		Y	Y	10/16/2006
	16		Y	Y	09/21/2006
	14		Y	Y	09/27/2006
	18		Y	Y	10/08/2006
	14		Y	Y	10/05/2006
	16		Y	Y	10/03/2006
	03		Y	Y	10/23/2006
	04		Y	Y	12/08/2006
	16		Y	Y	11/02/2006

(b) (6)		(b) (6)			
	16		Y	Y	10/26/2006
	18		Y	Y	11/12/2006
	16		Y	Y	09/22/2006
	04		Y	Y	11/29/2006
	04		Y	Y	11/30/2006
	16		Y	Y	11/14/2006
	16		Y	Y	11/20/2006
	16		Y	Y	11/22/2006
	18		Y	Y	11/12/2006
	03		Y	Y	11/06/2006
	18		Y	Y	11/17/2006
	14		Y	Y	11/17/2006
	04		Y	Y	12/01/2006
	03		Y	Y	11/28/2006
	25		Y	Y	12/22/2006
	25		Y	Y	11/10/2006
	18		Y	Y	12/09/2006
	15		Y	Y	12/28/2006
	25		Y	Y	12/07/2006
	18		Y	Y	12/22/2006
	25		Y	Y	11/27/2006
	25		Y	Y	01/04/2007
	23		Y	Y	11/28/2006
	18		Y	Y	12/09/2006
	25		Y	Y	12/07/2006
	23		Y	Y	12/27/2006
	16		Y	Y	01/16/2007
	15		Y	Y	12/13/2006
	25		Y	Y	01/05/2007
	18		Y	Y	12/23/2006
	18		Y	Y	12/27/2006
	18		Y	Y	12/25/2006
	04		Y	Y	02/19/2007
	16		Y	Y	01/19/2007
	16		Y	Y	02/07/2007
	18		Y	Y	02/08/2007
	03		Y	Y	12/28/2006
	16		Y	Y	01/17/2007
	18		Y	Y	02/04/2007
	15		Y	Y	02/13/2007
	16		Y	Y	01/15/2007
	16		Y	Y	01/19/2007
	25		Y	Y	01/22/2007
	16		Y	Y	02/28/2007

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich
Subject: Re: SUPPORT
Date: Thursday, February 28, 2008 1:41:56 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> We are missing a few support outcomes. Please let us know how you are doing.
>
> Thanks for all the effort!!!
> Rose
>
> | CENTER | NETWORK | ROP_message |
> |---|---|---|
> | 13 | (b) (6) | 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
> | 13 | (b) (6) | 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. |
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine
> NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (For overnight delivery, use Rockville, MD 20852)
> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

Baby 73771 has an eye exam scheduled at our site for 3/3 so we should have some results then. The other baby as I told you before has not been reachable- transferred to another hospital then home. The baby did very well, both eye exams showed no ROP but only one exam had vessels to zone 3. We will keep trying to reach the family.
Monica

From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT and inositol trials
Date: Wednesday, February 27, 2008 4:25:57 PM

---

ok...I"ll get him to the public site at this point..but no further

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/27/2008 03:21 PM

To: "Michael Cotten" <cotte010@mc.duke.edu>
cc:
Subject: RE: SUPPORT and inositol trials

correct

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, February 27, 2008 3:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT and inositol trials

Ok

Not the private gateway correct??

MC

----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD) [E]" [higginsr@mail.nih.gov]
Sent: 02/27/2008 11:50 AM EST
To: Michael Cotten
Cc: Ronald Goldberg
Subject: RE: SUPPORT and inositol trials

Mike
For the time being, I would refer him to the network website at
https://neonatal.rti.org/
Once I get something formal in writing, we can likely share the
protocols
Thanks
Rose

-----Original Message-----
From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Wednesday, February 27, 2008 11:23 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg
Subject: Fw: SUPPORT and inositol trials

HI Rose,,

Matt Laughon from UNC is requesting taking a look at the active study
protocols (see email below). As we explore this association with UNC as
a
secondary site, may I share the current full protocols for active
Network
trials with the site's potential PI for Network studies that would start
up
in the near future if everything works out?

thanks

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu
----- Forwarded by Michael Cotten/Pediatrics/mc/Duke on 02/27/2008 11:16
AM

"Matt Laughon"

<Matt_Laughon@med

.unc.edu>

To

"'Michael Cotten'"

02/27/2008 09:26 <cotte010@mc.duke.edu>

AM

cc

Subject

SUPPORT and inositol trials

Hi Mike,

In anticipation of joining as a satellite, would you mind sharing the protocols that will be ongoing in the next six months? You mentioned SUPPORT and inositol, are there others?

The reason I ask is that we have a history of separating the clinical team
from the research team, and the SUPPORT trial in particular will need the
buy-in from fellows and attendings taking call at night. We have a business meeting this afternoon and I have some time set aside to discuss
this issue.

Thanks,

Matt

Matthew M. Laughon, MD, MPH
Division of Neonatal/Perinatal Medicine
Department of Pediatrics
The University of North Carolina at Chapel Hill
CB# 7596, 4th Floor, UNC Hospital

Chapel Hill, NC 27599-7596
Office: (919) 966-5063
Facsimile: (919) 966-3034

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Pablo Sanchez; Roy Heyne
Subject: Re: SUPPORT
Date: Tuesday, February 26, 2008 6:33:31 PM

Rose,
ROP data for (b) (6) is in the computer and will be transmitted today.
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/21/2008 2:52 PM >>>
Hi,

We are missing a few support outcomes. Please let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

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Bethesda, MD 20892

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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Pickett, James; Finer, Neil
Subject: FW: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Date: Tuesday, February 26, 2008 1:09:59 PM

Hi everyone,

Below is the word from Masimo re: oximeter downloads on Friday. If James and Marie could double-check the downloads which include Friday or Saturday that would be great. I guess now they have 9 months to figure out what they did to their own equipment.

Thanks,
Wade

-----Original Message-----
From: Dave Baker [mailto:dbaker@masimo.com]
Sent: Tuesday, February 26, 2008 9:20 AM
To: Rich, Wade; Maribeth Sayre; Finer, Neil; williamtm@med.usyd.edu.au; Alpana Ghadge; Rikki Mills; Jim Litchfield; brian.darlow@otago.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; Lorrie Costantini; Stacey Taggart; shey@easynet.co.uk; Breidge Boyle; Michelle Gabriel; Paul Cornick
Cc: Michael OReilly; Chris Novak; Stephen Taylor; Valerie Begnoche; Phil Weber
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters

Wade et al,

I'm was just told by our software team that this Friday (Leap Day) there shouldn't be any problems downloading this data. There should be no other problems of this sort expected until New Years Eve of this year. We are working feverishly for a solution to this issue.

Dave Baker
Director of Clinical Research - Project Management
direct: (949) 297-7314
cell: (949) 697-(b) (6)
email: dbaker@masimo.com

-----Original Message-----
From: Rich, Wade [mailto:wrich@pedsmail.ucsd.edu]
Sent: Tuesday, February 26, 2008 8:34 AM
To: Maribeth Sayre; Finer, Neil; williamtm@med.usyd.edu.au; Alpana Ghadge; Rikki Mills; Jim Litchfield; brian.darlow@otago.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; Lorrie Costantini; Stacey Taggart; shey@easynet.co.uk; Breidge Boyle; Michelle Gabriel; Paul Cornick
Cc: Michael OReilly; Chris Novak; Stephen Taylor; Valerie Begnoche; Dave Baker; Phil Weber
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters

Maribeth et al.

We are 3 days from the end of the month. Do we have any idea what will happen to the data for all of the SUPPORT/BOOST infants on February 29-March 1st ?

Wade

From: Maribeth Sayre [mailto:msayre@masimo.com]
Sent: Thursday, February 21, 2008 5:58 PM
To: Finer, Neil; Rich, Wade; williamtm@med.usyd.edu.au; Alpana Ghadge; Rikki Mills; Jim Litchfield; brian.darlow@otago.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; Lorrie Costantini; Stacey Taggart; shey@easynet.co.uk; Breidge Boyle; Michelle Gabriel; Paul Cornick
Cc: Michael OReilly; Chris Novak; Stephen Taylor; Valerie Begnoche; Dave Baker; Phil Weber
Subject: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Importance: High

Hello all,

There is a problem with the data from Jan 1, 2008 on the study masked oximeters. It was first noted by Dr Edmund Hey in the UK, and has subsequently been seen in SUPPORT babies in the US. The data on Jan 1, 2008 is repetition of a single bit of data for the whole 24 hours. The data on Jan 2, 2008 is a standard recording. There is some question as to whether the data recorded on Jan 2 is actually the data from Jan 1 (misaligned data/date) or whether the data from Jan 1, 2008 is lost. The problem seems to be related to Leap Year. Masimo has been trying to duplicate the problem, but has not been able to reproduce this error during testing of both standard and masked Radicals.

We have contacted UCSD, where they have found the problem in masked Radicals. Tomorrow, Feb 22, we will pick up one of the affected masked Radicals from UCSD, along with a standard Radical with the same problem. We will bring these Radicals back to Irvine for testing. As soon as we have results from these tests, I will send them to you. We are looking for answers to the following questions:

1. Is the data recorded on Jan 2, 2008 actually data from that date, or is it the data from Jan 1? (Misaligned data/date problem)

2. If the data recorded on Jan 2, 2008 is from Jan 2, what happened to the data from Jan 1, 2008? (Lost data)
3. If the data from Jan 1, 2008 is lost, is it recoverable?
4. If there is a Misalignment of data and date, how can it be corrected?
5. What will happen on Feb 29, 2008 and Mar 1, 2008?

6. What caused the problem? How can we fix it?

I apologize to all of you for this problem. I am very aware of how serious it is. We have 2 teams of technical and engineering people working on this. We will get information to you as soon as we have it.

I do have a request. Could all of you who have identified this problem in your NICUs please send me the serial numbers of the affected oximeters? We suspect that all of the masked oximeters may be involved, but don't know if this is true.

Please be assured we are working diligently to identify the error and correct it. And please accept my regrets for all the difficulty this has caused.

Please let me know if you have questions. Unfortunately I will be out of the office on sick leave for the next 5 days, but I will answer emails as soon as possible. For technical issues, please contact Chris Novak at: cnovak@Masimo.com

For all other issues, please contact Valerie Begnoche at:
vbegnoche@Masimo.com
or Dave Baker at:
dbaker@Masimo.com
Please copy me on all emails, as usual.

Thank you all for your patience and understanding.

Best regards,
Maribeth

****

From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, February 26, 2008 7:50:28 AM

Rsoe,
I am so sorry these are delayed. The eye exam patient is scheduled, however she has been i the hospital more than out and has missed several appointment d/t hospital stays. The other two have been done, I have been out (b) (6) (b) (6) and will get this data entered as soon as possible.
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/21/08 2:52 PM >>>
Hi,

We are missing a few support outcomes. Please let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU marked as complete (per NF10/SF10) but NF09a has not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poindexter, Brenda B
Subject: RE: SUPPORT
Date: Monday, February 25, 2008 3:42:38 PM

Hi. Yes, we are still following this infant. They have not come in for their most likely final appt.

Thank you-

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.274.8963 (fax)
317.312.(b)(6)1 (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2008 4:21 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few support outcomes. Please let us know how you are doing.

Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Re: Secondary proposal to SUPPORT MRI secondary
Date: Monday, February 25, 2008 1:20:25 PM

Hi Rose

I just left you a message re: Goldstein proposal. I think I have cc'd you my responses to her with my comments and concerns about the proposal. Please let me know if there is something brewing under the surface that I should know about or I should address. I told Ricki in response to this email that I would be very happy to meet with her and her fellow at the SPR to talk further and discuss ideas

Susan

X-Sieve: CMU Sieve 2.3
Delivered-To: srhintz@stanford.edu
To: Susan Hintz <srhintz@stanford.edu>
Cc: higginsr@mail.nih.gov
Subject: Re: Secondary proposal to SUPPORT MRI secondary
From: Ricki F Goldstein <golds005@mc.duke.edu>
Date: Fri, 22 Feb 2008 08:33:01 -0500

Susan,
Thanks for taking the time when you are so busy to point out these important issues. You have clearly had the opportunity to investigate all the problems of how data is collected in pursuing your own research questions. I first realized that the documentation of laterality of Grade 4 IVH was missing when I tried to do my IVH/GA analyses which led to the enhancement of data collection in 2006. Now, in writing the manuscript, I have to point that out as a weakness, but the results are still somewhat interesting, I think. I am going to discuss your comments today with the fellow from UNC that I am mentoring who originally raised the research questions of detailing grade 4's using Bassan's method in predicting outcome. I will get back to you next week with a refined proposal for the subset of support MRI participants, which, as you say, will likely only be a fraction of the total kids with grade 4's. You are right, that the proposal I sent is for a larger cohort. Rose and I were trying to figure out ways of decreasing cost for our proposal and thought that, since the MRI group was already having a detailed look at their CUS by a central reader, that perhaps a few extra descriptive details could be added to these readings. Then additional money could be rquested for the extra babies not in the SUPPORT study, but in GDB follow-up, for the readings. And then the final kids are those not in GDB follow-up but whose IVH data is still collected in the GDB. These would need money for both central readings and follow-up. I'm sorry I didn't make that clear at the beginning. .
On a side note, it would be great if you, my fellow (Natalie Matre) and I could have coffee one day at the SPR and discuss our common interests. Natalie may or may not be at a Network Center next year, but she certainly would benefit from meeting you and having you for a contact/collaborator/consultant in the future. Have a great weekend. Hope you're not on call so can enjoy it.
Ricki

Ricki F. Goldstein MD
Associate Professor of Pediatrics
Director, High-Risk Infant Follow-up Program and

Special Infant Care Clinic
Division of Neonatology
Box 3179, Duke University Medical Center
Durham, NC 27710
office: 919-681-6024
pager: 919-970(b) (6)
fax: 919-681-4836

Susan Hintz <srhintz@stanford.edu>

02/22/2008 02:17 AM

To

Ricki F Goldstein <golds005@mc.duke.edu>

cc

higginsr@mail.nih.gov

Subject

Re: Secondary proposal to SUPPORT MRI secondary

Hi Ricki

I am replying again now that I am finally at home from the NICU. Here are some additional thoughts -

1) First, I want to clarify - the proposal you sent me was for a larger study (prospective throughout the Network estimated to last until 2009). I think I did comment in my first paragraph on 2/13 what I thought the issues might be on that from the Steering Committee perspective - particularly money issues. I did not receive a specific "tertiary" study idea for the SUPPORT Neuroimaging secondary - but I thought you were just kicking the idea around. I guess if you decided to go forward with that, you would need to present to the steering committee

2) SUPPORT Neuroimaging secondary - as I said in my earlier email, we have a central reading form for the cranial US reads. There is quite a bit of information detailed in this form, and I think it would address the details you want from G. Methods in your proposal. The form was developed with input from Seetha Shankaran as well. I am attaching it.

But as I said in my 2/13 email, I would estimate we would have probably only ~50 patients with "grade 4" in the SUPPORT neuroimaging secondary. It seems that you have estimated you would have 191 infants with grade 4 over a 3 year

period in your overall Network proposal. Have you talked with RTI to find a way to estimate the number of patients you would need to answer the questions you have?

3) It looks like your primary goal is looking at the outcomes of unilateral vs. bilateral parenchymal hemorrhages - as you said, you would have to wait a while to get follow-up on these patients, but it seems that your "estimated recruitment period" takes this into account. Given that the bilateral parenchymal bleed question has been added to the GDB, this primary goal would seem an inexpensive "first cut", albeit one that would take a while.

4) The more expensive thing is what I understand to be your second goal - looking at additional CUS information and applying it to refine prognosis for (only unilateral?) intraparenchymal hemorrhages. Would you be planning on using the Bassan system exactly? You have a list of details you would suggest collecting, but it is not clear whether you are planning on developing your own system or applying a "known" system? How would you choose the "point score" or similar for the important details for the system - CART analysis, logistic regression? If you decided to do that for the entire Network, it would be expensive to collect the additional information, but on the flip side, the SUPPORT Neuroimaging secondary would have significantly fewer patients. Also, you know that we would not even finish enrollment of the SUPPORT trial until mid-next year, so that would mean we would not have neurodevelopmental follow-up data on our secondary cohort until 18-22++ months from that time. So you would have to wait for the SUPPORT centrally read data too -

5) I am also concerned about the variability in how CUS are obtained in the Network. Not every site is doing routine mastoid and posterior fontanelle views (at least they weren't the last time I asked). As you know, the lack of these views will substantially limit the ability to see potentially very important isolated parenchymal hemorrhages. Even the diagnosis of "grade 4" seems variable - even among central readers. Isolated parenchymal hemorrhages (i.e., without ipsilateral intraventricular hemorrhage) were not consistently graded as "grade 4" in the PiNO CUS reliability and accuracy study. So isolated cerebellar hemorrhages or peripheral cortical hemorrhages for instance were not necessarily called the same thing by different radiologists. Concerning...

OK - I am now being paged again so I will have to sign off. Sorry -

Susan

I Susan,

Have you had a chance to look at this further? I need to let Rose know if I will present a "new" concept in April or if I will be proposing a secondary to an existing study. I realize that there will be more babies to look at prospectively in the GDB, but it will take several years for babies starting in 2006 to gert followed up. Just to clarify, I know that your study is looking at comparing early US to discharge MRI. The question here would be to add the detailed reading of head ultrasound in your cohort with grade 4 IVH (if your central reader would be willing describe these in as bit more detail than usual). Our hypothesis, uinlike yours, is that this more extensive reading of th early CUS (unlike the traditional way of reporting pathology) will be as predictive as the discharge MRI and certainly more useful to parents in making decisions about aggressiveness of care. Of course you

would be included as an author on this additional aspect of US interpretation. Hope to talk to you soon.
Ricki

Ricki F. Goldstein MD
Associate Professor of Pediatrics
Director, High-Risk Infant Follow-up Program and
Special Infant Care Clinic
Division of Neonatology
Box 3179, Duke University Medical Center
Durham, NC 27710
office: 919-681-6024
pager: 919-970(b) (6)
fax: 919-681-4836
Susan Hintz <srhintz@stanford.edu>
02/13/2008 01:08 PM

To
Ricki F Goldstein <golds005@mc.duke.edu>
cc
Subject
Re: Secondary proposal to SUPPORT MRI secondary

Hi Ricki

Good to hear from you! I have not looked this over in GREAT detail yet, but of course I am very interested in your concept - I think you and I share many concerns about prediction of outcomes with respect to CUS data.
Congratulations to you and your fellow for having your work accepted as a platform presenation! Really exciting, and I look forward to hearing the presentation -

Overall, I think the issue will be low numbers of patients with grade 4 in the SUPPORT neuroimaging and outcomes secondary. I know that part of your question is extent of bleed and other variables that would require a central reader, but have you considered proposing a sort of "first cut" question using the locally-read GDB data and 18-22 month follow-up? I know we don't have GDB data about laterality before January 2006, so that means you would have to wait for follow-up, but this could be a great first step with much bigger numbers. I think if you try to pitch a separate cohort with central reading right off, it could be refused on the basis of cost. BUT, if you had really intriguing results with the GDB data, you might be able to convince folks at least to have a time-limited additional data collection for your more detailed questions about extent of bleed, midline shift, etc. Also, the accuracy and reliability analysis I did can reassure you about the accuracy of local readers with respect to grade 4 compared with central readers - sensitivity was 82-86% and specificity was 92-95% for grade 4.

Just to give you some numbers/answers quickly -

1) Percentage of babies in SUPPORT enrolled in neuroimaging and outcome

secondary? This is a sort of tough question to answer precisely, because enrollment in the secondary occurs at different times in different centers. But, given the enrollment to date, we are estimating that there will be 350-400 surviving infants with complete neuroimaging - these are the group that will have central reading of everything. So, if the network numbers in the past hold true, that will only give around 40-50 patients with any grade 4.

2) How many babies have grade 4 in the SUPPORT secondary now? I can't answer that, but look at estimates above. First, the CUS central reading is not underway yet - the central readers don't want to do the same type of rolling reading as the MRI. Second, I would not be able to know that anyway because it is a DSMC thing. They are looking at those kinds of safety issues via local reader data, but I suspect it is not much different from the baseline expected GDB data or they would have had concerns. Thus, refer to my estimate in #1.

3) Comparing early US and MRI for prediction of ND outcome - This is already pretty much the central question in my secondary, so I don't think it could be included in other associated studies.

I will talk with you further as I look at the proposal in more detail -

Susan

Hi Susan,
Hope things are going well for you. Attached is a concept proposal for a study that I and a 3rd year fellow who I have been mentoring would like to propose as a secondary to your MRI secondary to SUPPORT.As you will see, it was originally written to include all babies with Grade 4 IVH followed by GDB. However, Rose suggested that it be proposed as a secondary to your MRI study since those ultrasounds are already being copied and read and the babies are being followed. The proposal does not presently include comparison of prediction of outcome by the detailed analysis of early head US versus discharge MRI, but if it is going to be a secondary to your study, we will include that research question as well. If numbers in SUPPORT are too small, some of the babies could be enrolled via a secondary to SUPPORT, others through the GDB follow-up study and then the rest who have GDB data could be followed as an addtional cohort. It may get complicated. Obviously, the best shot at getting the Network to fund the study is to concentrate on those babies who are presenly being followed

anyway. As you will see, the budget cannot really be finalized until I find out what percentage of the babies would likely be enrolled in GDB follow-up (< or equal to 26 weeks) or SUPPORT +/- the MRI secondary). I got the total numbers of Grade 4 IVH in 2006 from the GDB book, but I can't tell how many of these are older than 26 weeks and not in SUPPORT. I also don't know how many of the SUPPORT babies with actually have Grade 4 IVH and of those, how many have gotten MRI's. So, I need to know a couple of things from you. First, what do you think of the proposal and would you consider it as a secondary to your MRI secondary? (Does that make it a tertiary study??) Second, do you know what percentage of babies in SUPPORT are getting

enrolled in the MRI study? And, third, do you have any idea how many babies who have gotten MRI's so far have Grade 4 IVH? Maybe you could look through the study proposal and then we could talk on the phone. THanks very much. The fellow involved just got an abstract accepted (as a platform) on the data collected from a couple of centers in North Carolina concerning laterality of bleeds. The more extensive reading of the early head ultrasounds from this cohort is available yet.
Ricki

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pager: 919-970(b) (6)
fax: 919-681-4836

(See attached file: IVH NICHD proposal.doc)
Attachment converted: Macintosh HD:IVH NICHD proposal.doc (WDBN/«IC») (00CF9173)

--

Susan R. Hintz, M.D., M.S. Epi
Associate Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
750 Welch Road, Suite 315
Palo Alto, CA 94304
ph: 650-723-5711
fax: 650-725-8351[attachment "Central ReaderCranial US[MRI04]6-7-05.doc" deleted by Ricki F Goldstein/Pediatrics/mc/Duke]

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Monday, February 25, 2008 8:55:51 AM

The last exam we currently have for that infant is from 10/12/07. Since the data from the 2/15/08 exam were entered on Thursday of last week, we should receive the data in the download from the center tomorrow.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 25, 2008 8:46 AM
To: Gantz, Marie
Cc: Das, Abhik
Subject: Fw: SUPPORT

Is this in the system?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Elizabeth Billian <du2744@wayne.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Becky Bara <rbara@med.wayne.edu>; Beena Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>
Sent: Mon Feb 25 08:30:19 2008
Subject: Re: SUPPORT

Hi,

Thanks for the email. NW(b) (6) reached her final outcome on 2/15/08; both eyes are mature. Data was entered 2/21/08.

Betty Billian

---- Original message ----
>Date: Thu, 21 Feb 2008 15:54:38 -0500
>From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>Subject: SUPPORT
>To: "Shankaran, Seetha" <sshankar@med.wayne.edu>, "Beena Sood" <bsood@med.wayne.edu>, "Elizabeth Billian" <du2744@wayne.edu>, <ae5357@wayne.edu>, <apappas@med.wayne.edu>
>Cc: "Gantz, Marie" <mgantz@rti.org>, "Das, Abhik" <adas@rti.org>
>
> Hi,
>

> We are missing a few support outcomes. Please let
> us know how you are doing.
>
>
>
> Thanks for all the effort!!!
> Rose
>
> CENTER NETWORK ROP_message
> 50 weeks PMA has been reached and
> final ROP exam status has not been
> reported on the SUPP10 for either
> 5 (b) (6) eye.
>
>
>
>
>
>
> Rosemary D. Higgins, M.D.
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal
> Medicine
>
> NICHD, NIH
>
> 6100 Executive Blvd., Room 4B03B
>
> MSC 7510
>
> Bethesda, MD 20892
>
> (For overnight delivery, use Rockville, MD 20852)
>
> 301-435-7909
>
> 301-496-3790 (FAX)
>
> higginsr@mail.nih.gov
>
>

From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, February 22, 2008 3:46:20 PM

The follow-up baby has an appointment on 2/28. The others have been taken care of and will be transmitted on Tuesday.
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 2/21/2008 3:26 PM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few support outcomes. Please let us know how you are doing.
This is phenomenal given your superior recruitment!!!
Thanks for all the effort!!!
Rose

CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
CENTER	NETWORK	BPD_message
16	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
CENTER	NETWORK	ROP_message
16	(b) (6)	SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Susan Hintz
To: Ricki F Goldstein
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Secondary proposal to SUPPORT MRI secondary
Date: Friday, February 22, 2008 2:17:20 AM
Attachments: Central ReaderCranial US[MRI04]6-7-05.doc

Hi Ricki

I am replying again now that I am finally at home from the NICU. Here are some additional thoughts -

1) First, I want to clarify - the proposal you sent me was for a larger study (prospective throughout the Network estimated to last until 2009). I think I did comment in my first paragraph on 2/13 what I thought the issues might be on that from the Steering Committee perspective - particularly money issues. I did not receive a specific "tertiary" study idea for the SUPPORT Neuroimaging secondary - but I thought you were just kicking the idea around. I guess if you decided to go forward with that, you would need to present to the steering committee

2) SUPPORT Neuroimaging secondary - as I said in my earlier email, we have a central reading form for the cranial US reads. There is quite a bit of information detailed in this form, and I think it would address the details you want from G. Methods in your proposal. The form was developed with input from Seetha Shankaran as well. I am attaching it.

But as I said in my 2/13 email, I would estimate we would have probably only ~50 patients with "grade 4" in the SUPPORT neuroimaging secondary. It seems that you have estimated you would have 191 infants with grade 4 over a 3 year period in your overall Network proposal. Have you talked with RTI to find a way to estimate the number of patients you would need to answer the questions you have?

3) It looks like your primary goal is looking at the outcomes of unilateral vs. bilateral parenchymal hemorrhages - as you said, you would have to wait a while to get follow-up on these patients, but it seems that your "estimated recruitment period" takes this into account. Given that the bilateral parenchymal bleed question has been added to the GDB, this primary goal would seem an inexpensive "first cut", albeit one that would take a while.

4) The more expensive thing is what I understand to be your second goal - looking at additional CUS information and applying it to refine prognosis for (only unilateral?) intraparenchymal hemorrhages. Would you be planning on using the Bassan system exactly? You have a list of details you would suggest collecting, but it is not clear whether you are planning on developing your own system or applying a "known" system? How would you choose the "point score" or similar for the important details for the system - CART analysis, logistic regression? If you decided to do that for the entire Network, it would be expensive to collect the additional information, but on the flip side, the SUPPORT Neuroimaging secondary would have significantly fewer patients. Also, you know that we would not even finish enrollment of the SUPPORT trial until mid-next year, so that would mean we would not have neurodevelopmental follow-up data on our secondary cohort until 18-22++ months from that time. So you would have to wait for the SUPPORT centrally read data too -

5) I am also concerned about the variability in how CUS are obtained in the Network. Not

every site is doing routine mastoid and posterior fontanelle views (at least they weren't the last time I asked). As you know, the lack of these views will substantially limit the ability to see potentially very important isolated parenchymal hemorrhages. Even the diagnosis of "grade 4" seems variable - even among central readers. Isolated parenchymal hemorrhages (i.e., without ipsilateral intraventricular hemorrhage) were not consistently graded as "grade 4" in the PiNO CUS reliability and accuracy study. So isolated cerebellar hemorrhages or peripheral cortical hemorrhages for instance were not necessarily called the same thing by different radiologists. Concerning...

OK - I am now being paged again so I will have to sign off. Sorry -

Susan

I Susan,
Have you had a chance to look at this further? I need to let Rose know if I will present a "new" concept in April or if I will be proposing a secondary to an existing study. I realize that there will be more babies to look at prospectively in the GDB, but it will take several years for babies starting in 2006 to gert followed up. Just to clarify, I know that your study is looking at comparing early US to discharge MRI. The question here would be to add the detailed reading of head ultrasound in your cohort with grade 4 IVH (if your central reader would be willing describe these in as bit more detail than usual). Our hypothesis, uinlike yours, is that this more extensive reading of th early CUS (unlike the traditional way of reporting pathology) will be as predictive as the discharge MRI and certainly more useful to parents in making decisions about aggressiveness of care. Of course you would be included as an author on this additional aspect of US interpretation. Hope to talk to you soon.

Ricki

Ricki F. Goldstein MD
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fax: 919-681-4836

Susan Hintz <srhintz@stanford.edu>

02/13/2008 01:08 PM

To

Ricki F Goldstein <golds005@mc.duke.edu>

cc

Subject

Re: Secondary proposal to SUPPORT MRI secondary

Hi Ricki

Good to hear from you! I have not looked this over in GREAT detail yet, but of course I am very interested in your concept - I think you and I share many concerns about prediction of outcomes with respect to CUS data.
Congratulations to you and your fellow for having your work accepted as a platform presenation! Really exciting, and I look forward to hearing the presentation -

Overall, I think the issue will be low numbers of patients with grade 4 in the SUPPORT neuroimaging and outcomes secondary. I know that part of your question is extent of bleed and other variables that would require a central reader, but have you considered proposing a sort of "first cut" question using the locally-read GDB data and 18-22 month follow-up? I know we don't have GDB data about laterality before January 2006, so that means you would have to wait for follow-up, but this could be a great first step with much bigger numbers. I think if you try to pitch a separate cohort with central reading right off, it could be refused on the basis of cost. BUT, if you had really intriguing results with the GDB data, you might be able to convince folks at least to have a time-limited additional data collection for your more detailed questions about extent of bleed, midline shift, etc. Also, the accuracy and reliability analysis I did can reassure you about the accuracy of local readers with respect to grade 4 compared with central readers - sensitivity was 82-86% and specificity was 92-95% for grade 4.

Just to give you some numbers/answers quickly -

1) Percentage of babies in SUPPORT enrolled in neuroimaging and outcome secondary? This is a sort of tough question to answer precisely, because enrollment in the secondary occurs at different times in different centers. But, given the enrollment to date, we are estimating that there will be 350-400 surviving infants with complete neuroimaging - these are the group that will have central reading of everything. So, if the network numbers in the past hold true, that will only give around 40-50 patients with any grade 4.

2) How many babies have grade 4 in the SUPPORT secondary now? I can't answer that, but look at estimates above. First, the CUS central reading is not underway yet - the central readers don't want to do the same type of rolling reading as the MRI. Second, I would not be able to know that anyway because it is a DSMC thing. They are looking at those kinds of safety issues via local reader data, but I suspect it is not much different from the baseline expected GDB data or they would have had concerns. Thus, refer to my estimate in #1.

3) Comparing early US and MRI for prediction of ND outcome - This is already pretty much the central question in my secondary, so I don't think it could be included in other associated studies.

I will talk with you further as I look at the proposal in more detail -

Susan

Hi Susan,
Hope things are going well for you. Attached is a concept proposal for a study that I and a 3rd year fellow who I have been mentoring would like to propose as a secondary to your MRI secondary to SUPPORT.As you will see, it was originally written to include all babies with Grade 4 IVH followed by GDB. However, Rose suggested that it be proposed as a secondary to your MRI study since those ultrasounds are already being copied and read and the babies are being followed. The proposal does not presently include comparison of prediction of outcome by the detailed analysis of early head US versus discharge MRI, but if it is going to be a secondary to your study, we will include that research question as well. If numbers in

SUPPORT are too small, some of the babies could be enrolled via a secondary to SUPPORT, others through the GDB follow-up study and then the rest who have GDB data could be followed as an addtional cohort. It may get complicated. Obviously, the best shot at getting the Network to fund the study is to concentrate on those babies who are presenly being followed anyway. As you will see, the budget cannot really be finalized until I find out what percentage of the babies would likely be enrolled in GDB follow-up (< or equal to 26 weeks) or SUPPORT +/- the MRI secondary). I got the total numbers of Grade 4 IVH in 2006 from the GDB book, but I can't tell how many of these are older than 26 weeks and not in SUPPORT. I also don't know how many of the SUPPORT babies with actually have Grade 4 IVH and of those, how many have gotten MRI's. So, I need to know a couple of things from you. First, what do you think of the proposal and would you consider it as a secondary to your MRI secondary? (Does that make it a tertiary study??) Second, do you know what percentage of babies in SUPPORT are getting enrolled in the MRI study? And, third, do you have any idea how many babies who have gotten MRI's so far have Grade 4 IVH? Maybe you could look through the study proposal and then we could talk on the phone. THanks very much. The fellow involved just got an abstract accepted (as a platform) on the data collected from a couple of centers in North Carolina concerning laterality of bleeds. The more extensive reading of the early head ultrasounds from this cohort is available yet.
Ricki

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fax: 919-681-4836

(See attached file: IVH NICHD proposal.doc)
Attachment converted: Macintosh HD:IVH NICHD proposal.doc (WDBN/«IC») (00CF9173)

--

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NICU Network

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Support Neuroimaging Secondary
Draft Central Cranial US Reading Form

MRI04 Rel 1
June 7, 2005

Center: Network No: Birth No

A. IDENTIFICATION

1. READER: ___ ___ ___ INITIALS
2. DATE READ: __ __/__ __/__ __ __ __ MONTH DAY YEAR
3. READING: ____
4. DATE OF SONOGRAM: ___ ___/___ ___/___ ___ ___ ___

5. QUALITY: GOOD POOR
6. READABLE: YES NO
8. ALL NECESSARY VIEWS AVAILABLE: YES NO
9. NORMAL READING: YES NO

ULTRASOUND RESULTS	Left		Right	
	Yes	No	Yes	No
B. ECHODENSITY SITE				
1. Echodensity present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intraventricular				
1) If Yes,				
< 25 % filled				
25-50 % filled				
> 50% filled				
d. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
5. Thalamus				
6. Posterior Fossa				
e. Other				

	Left		Right	
	Yes	No	Yes	No
C. ECHOLUCENCY SITE				
1. Echolucency present				
If Yes, mark all that apply				
a. Subependymal				
b. Periventricular (PVL)				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
c. Intracerebral				
If Yes, mark all that apply				
1. Frontal				
2. Temporal				
3. Parietal				
4. Occipital				
d. Parenchymal Cyst				
e. Other				
D. OTHER PARENCHYMAL				
1. Other Parenchymal				
If Yes, mark all that apply				
a. Calcification				
b. Cerebral edema				
c. Cortical atrophy				
d. Extra axial fluid				
e. Infarct				
f. LS Branching				
g. Other				

	Left		Right	
	Yes	No	Yes	No
E. VENTRICLES				
1. Ventricle abnormality				
a. If Yes,				
Mild increase				
Moderate increase				
Severe increase				
Slit Ventricles				
2. Choroid abnormality				
If Yes, mark all that apply				
a. Cyst				
b. Hemorrhage				
c. other				
F. HEMORRHAGE CLASSIFICATION				
1. Hemorrhage				
If Yes,				
a. Papile Classification				
Grade I				
Grade II				
Grade III				
Grade IV				
Indeterminate				
G. STRUCTURAL ABNORMALITIES				
1. Structural abnormality				
If Yes, comments:				

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT
Date: Friday, February 22, 2008 1:51:11 PM

No, we do not have data from Cincinnati on this child.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
919-541-6955

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 22, 2008 1:51 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: FW: SUPPORT

Did Cincinnati enter this child?

From: Bonnie Siner [mailto:bss5@case.edu]
Sent: Friday, February 22, 2008 1:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

I have already responded that (b) (6) was seen in Cincinnati ~8/07 by Teri Gratton– you should have the info from her.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2008 3:51 PM
To: mcw3@cwru.edu; nancy newman; Bonnie Siner; drfjcmd@aol.com
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT

Hi,
We are missing a few support outcomes. Please let us know how you are doing.
This is amazingly low given your stellar recruitment!!
Thanks for all the effort!!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
3	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Rich, Wade
To: Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Michael OReilly; msayre@masimo.com; cnovak@masimo.com; Dave Baker
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Date: Friday, February 22, 2008 12:05:40 PM

Chris et al.

I just spoke to Julie DiFiorre at Case Western and she has found this same problem on all of her Support oximeters, and to date none of her non-Support oximeters.
Wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 22, 2008 8:17 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Michael OReilly; Rich, Wade; msayre@masimo.com; cnovak@Masimo.com
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters

The following 7 oximeters were in use by the Neonatal Network on January 1, and all had the issue with repeated data.

311344
310932
310933
310989
310723
310748
310717

Marie

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

From: Maribeth Sayre [mailto:msayre@masimo.com]
Sent: Thursday, February 21, 2008 5:58 PM
To: Finer, Neil; Rich, Wade; williamtm@med.usyd.edu.au; Alpana Ghadge; Rikki Mills; Jim Litchfield; brian.darlow@otago.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; Lorrie Costantini; Stacey Taggart; shey@easynet.co.uk; Breidge Boyle; Michelle Gabriel; Paul Cornick
Cc: Michael OReilly; Chris Novak; Stephen Taylor; Valerie Begnoche; Dave Baker; Phil Weber
Subject: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Importance: High

Hello all,

There is a problem with the data from Jan 1, 2008 on the study masked oximeters. It was first noted by Dr Edmund Hey in the UK, and has subsequently been seen in SUPPORT babies in the US. The data on Jan 1, 2008 is repetition of a single bit of data for the whole 24 hours. The data on Jan 2, 2008 is a standard recording. There is some question as to whether the

data recorded on Jan 2 is actually the data from Jan 1 (misaligned data/date) or whether the data from Jan 1, 2008 is lost. The problem seems to be related to Leap Year. Masimo has been trying to duplicate the problem, but has not been able to reproduce this error during testing of both standard and masked Radicals.

We have contacted UCSD, where they have found the problem in masked Radicals. Tomorrow, Feb 22, we will pick up one of the affected masked Radicals from UCSD, along with a standard Radical with the same problem. We will bring these Radicals back to Irvine for testing. As soon as we have results from these tests, I will send them to you. We are looking for answers to the following questions:

1. Is the data recorded on Jan 2, 2008 actually data from that date, or is it the data from Jan 1? (Misaligned data/date problem)

2. If the data recorded on Jan 2, 2008 is from Jan 2, what happened to the data from Jan 1, 2008? (Lost data)
3. If the data from Jan 1, 2008 is lost, is it recoverable?
4. If there is a Misalignment of data and date, how can it be corrected?
5. What will happen on Feb 29, 2008 and Mar 1, 2008?
6. What caused the problem? How can we fix it?

I apologize to all of you for this problem. I am very aware of how serious it is. We have 2 teams of technical and engineering people working on this. We will get information to you as soon as we have it.

I do have a request. Could all of you who have identified this problem in your NICUs please send me the serial numbers of the affected oximeters? We suspect that all of the masked oximeters may be involved, but don't know if this is true.

Please be assured we are working diligently to identify the error and correct it. And please accept my regrets for all the difficulty this has caused.

Please let me know if you have questions. Unfortunately I will be out of the office on sick leave for the next 5 days, but I will answer emails as soon as possible. For technical issues, please contact Chris Novak at: cnovak@Masimo.com

For all other issues, please contact Valerie Begnoche at: vbegnoche@Masimo.com
or Dave Baker at: dbaker@Masimo.com
Please copy me on all emails, as usual.

Thank you all for your patience and understanding.

Best regards,
Maribeth

****

From: Gantz, Marie
To: Rich, Wade; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Michael OReilly; msayre@masimo.com; cnovak@masimo.com
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Date: Friday, February 22, 2008 12:04:09 PM

I checked that earlier – it did not happen last year.

Marie

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

From: Rich, Wade [mailto:wrich@pedsmail.ucsd.edu]
Sent: Friday, February 22, 2008 12:07 PM
To: Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Michael OReilly; msayre@masimo.com; cnovak@masimo.com
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters

marie,
We are all focusing on Leap Year. Can you check January 1, 2007 to make sure this did not happen then also?
wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, February 22, 2008 8:17 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Michael OReilly; Rich, Wade; msayre@masimo.com; cnovak@Masimo.com
Subject: RE: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters

The following 7 oximeters were in use by the Neonatal Network on January 1, and all had the issue with repeated data.

311344
310932
310933
310989
310723
310748
310717

Marie

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

From: Maribeth Sayre [mailto:msayre@masimo.com]
Sent: Thursday, February 21, 2008 5:58 PM
To: Finer, Neil; Rich, Wade; williamtm@med.usyd.edu.au; Alpana Ghadge; Rikki Mills; Jim Litchfield; brian.darlow@otago.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; Lorrie Costantini; Stacey Taggart; shey@easynet.co.uk; Breidge Boyle; Michelle Gabriel; Paul Cornick
Cc: Michael OReilly; Chris Novak; Stephen Taylor; Valerie Begnoche; Dave Baker; Phil Weber
Subject: Lost data vs misaligned data on Jan 1, 2008 on masked oximeters
Importance: High

Hello all,

There is a problem with the data from Jan 1, 2008 on the study masked oximeters. It was first noted by Dr Edmund Hey in the UK, and has subsequently been seen in SUPPORT babies in the US. The data on Jan 1, 2008 is repetition of a single bit of data for the whole 24 hours. The data on Jan 2, 2008 is a standard recording. There is some question as to whether the data recorded on Jan 2 is actually the data from Jan 1 (misaligned data/date) or whether the data from Jan 1, 2008 is lost. The problem seems to be related to Leap Year. Masimo has been trying to duplicate the problem, but has not been able to reproduce this error during testing of both standard and masked Radicals.

We have contacted UCSD, where they have found the problem in masked Radicals. Tomorrow, Feb 22, we will pick up one of the affected masked Radicals from UCSD, along with a standard Radical with the same problem. We will bring these Radicals back to Irvine for testing. As soon as we have results from these tests, I will send them to you. We are looking for answers to the following questions:

1. Is the data recorded on Jan 2, 2008 actually data from that date, or is it the data from Jan 1? (Misaligned data/date problem)

2. If the data recorded on Jan 2, 2008 is from Jan 2, what happened to the data from Jan 1, 2008? (Lost data)
3. If the data from Jan 1, 2008 is lost, is it recoverable?
4. If there is a Misalignment of data and date, how can it be corrected?
5. What will happen on Feb 29, 2008 and Mar 1, 2008?
6. What caused the problem? How can we fix it?

I apologize to all of you for this problem. I am very aware of how serious it is. We have 2 teams of technical and engineering people working on this. We will get information to you as soon as we have it.

I do have a request. Could all of you who have identified this problem in your NICUs please send me the serial numbers of the affected oximeters? We suspect that all of the masked oximeters may be involved, but don't know if this is true.

Please be assured we are working diligently to identify the error and correct it. And please accept my regrets for all the difficulty this has caused.

Please let me know if you have questions. Unfortunately I will be out of the office on sick leave for the next 5 days, but I will answer emails as soon as possible. For technical issues, please contact Chris Novak at: cnovak@Masimo.com

For all other issues, please contact Valerie Begnoche at: vbegnoche@Masimo.com
or Dave Baker at: dbaker@Masimo.com
Please copy me on all emails, as usual.

Thank you all for your patience and understanding.

Best regards,
Maribeth

****

From: Betty Vohr
To: Newman, Jamie
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Victoria Watson
Subject: RE: 2 SUPPORT patients with Bayley II rather than Bayley III
Date: Friday, February 22, 2008 11:15:26 AM

They both have MDIs substantially less than 70 which would put them in the NDI category. Also, one of the has a PDI of 50 which would qualify. I was under the impression that we put the lowest score as 49 not 50.
Betty Vohr

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Thursday, February 21, 2008 4:23 PM
To: Betty Vohr
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: 2 SUPPORT patients with Bayley II rather than Bayley III

Betty,
Do you have any suggestions for the two SUPPORT patients detailed below that received the Bayley II rather than the Bayley III?
Thanks, Jamie

From: Das, Abhik
Sent: Thursday, February 21, 2008 4:17 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Newman, Jamie
Cc: Gantz, Marie
Subject: RE: 2 SUPPORT patients with Bayley II rather than Bayley III

Yes, they are impaired. We can contact Betty to see what she thinks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2008 4:16 PM
To: Newman, Jamie
Cc: Gantz, Marie; Das, Abhik
Subject: RE: 2 SUPPORT patients with Bayley II rather than Bayley III

It would be nice if we can get the Bayley III. If not, these both appear Impaired to me, correct?
Should we send to Betty to see if she has any suggestions?
Thanks
Rose

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Thursday, February 21, 2008 3:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Das, Abhik
Subject: 2 SUPPORT patients with Bayley II rather than Bayley III

Rose,
The coordinator from Dallas (Janet Morgan) contacted me yesterday about a SUPPORT patient that had the Bayley 2 at follow-up rather than the Bayley 3. We looked at the data and have identified 2 SUPPORT patients (Center 4 Network Number (b) (6) and Center 12 Network Number (b) (6) that have a Bayley 2 rather than a Bayley 3 at follow-up.

Survey ID Number	Network Number	RS Center	Follow-up Number	Delivery Date	Birth Date	Birth Adjusted Age	Wt	Ht	Birth ID Code	Birth Adjusted Age	Birth Adjusted Age
4	(b) (6)	4	(b) (6)	(b) (6)	01/25/08	24	58	73	.	.	.
12		12			03/07/07	19	50	50	.	.	.

Please let me know how you would like to proceed.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Susan Hintz
To: Ricki F Goldstein
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Secondary proposal to SUPPORT MRI secondary
Date: Thursday, February 21, 2008 6:48:12 PM

Ricki

Have you seen the Cus central reading form? There is quite a bit of detailed information on that already. I guess it did not seem clear to me on reading the proposal how different the additional information needed would be and how different your hypothesis is from what we already have propsed in the support neuroimaging secondary. If you are focusing only on grade 4, I think that would be different. However, again I would be concerned about low numbers.

I did not know you had to present this separately at the meeting if you were using data already collected.

I am on service in the NICU so I have limited time. I can talk with you by phone if you want.

Susan

Sent from my iPhone

On Feb 21, 2008, at 2:25 PM, Ricki F Goldstein <golds005@mc.duke.edu> wrote:

> I Susan,
> Have you had a chance to look at this further? I need to let Rose know if I will present a "new" concept in April or if I will be proposing a secondary to an existing study. I realize that there will be more babies to look at prospectively in the GDB, but it will take several years for babies starting in 2006 to gert followed up. Just to clarify, I know that your study is looking at comparing early US to discharge MRI. The question here would be to add the detailed reading of head ultrasound in your cohort with grade 4 IVH (if your central reader would be willing describe these in as bit more detail than usual). Our hypothesis, uinlike yours, is that this more extensive reading of th early CUS (unlike the traditional way of reporting pathology) will be as predictive as the discharge MRI and certainly more useful to parents in making decisions about aggressiveness of care. Of course you would be included as an author on this additional aspect of US interpretation. Hope to talk to you soon.
> Ricki
>
> Ricki F. Goldstein MD
> Associate Professor of Pediatrics
> Director, High-Risk Infant Follow-up Program and
> Special Infant Care Clinic
> Division of Neonatology
> Box 3179, Duke University Medical Center
> Durham, NC 27710
> office: 919-681-6024
> pager: 919-970(b) (6)

fax: 919-681-4836

Susan Hintz <srhintz@stanford.edu>

02/13/2008 01:08 PM

To Ricki F Goldstein <golds005@mc.duke.edu>

cc

Subject Re: Secondary proposal to SUPPORT MRI secondary

Hi Ricki

Good to hear from you! I have not looked this over in GREAT detail yet, but of course I am very interested in your concept - I think you and I share many concerns about prediction of outcomes with respect to CUS data. Congratulations to you and your fellow for having your work accepted as a platform presenation! Really exciting, and I look forward to hearing the presentation -

Overall, I think the issue will be low numbers of patients with grade 4 in the SUPPORT neuroimaging and outcomes secondary. I know that part of your question is extent of bleed and other variables that would require a central reader, but have you considered proposing a sort of "first cut" question using the locally-read GDB data and 18-22 month follow-up? I know we don't have GDB data about laterality before January 2006, so that means you would have to wait for follow-up, but this could be a great first step with much bigger numbers. I think if you try to pitch a separate cohort with central reading right off, it could be refused on the basis of cost. BUT, if you had really intriguing results with the GDB data, you might be able to convince folks at least to have a time-limited additional data collection for your more detailed questions about extent of bleed, midline shift, etc. Also, the accuracy and reliability analysis I did can reassure you about the accuracy of local readers with respect to grade 4 compared with central readers - sensitivity was 82-86% and specificity was 92-95% for grade 4.

Just to give you some numbers/answers quickly -

1) Percentage of babies in SUPPORT enrolled in neuroimaging and outcome secondary? This is a sort of tough question to answer precisely, because enrollment in the secondary occurs at different times in different centers. But, given the enrollment to date, we are estimating that there will be 350-400 surviving infants with complete neuroimaging - these are the group that will have central reading of everything. So, if the network numbers in the past hold true, that will only give around 40-50 patients with any grade 4.

2) How many babies have grade 4 in the SUPPORT secondary now? I can't answer that, but look at estimates above. First, the CUS central reading is not underway yet - the central readers don't want to do the same type of rolling reading as the MRI. Second, I would not be able to know that anyway because it is a DSMC thing. They are looking at those kinds of safety issues via local

reader data, but I suspect it is not much different from the baseline expected GDB data or they would have had concerns. Thus, refer to my estimate in #1.

3) Comparing early US and MRI for prediction of ND outcome - This is already pretty much the central question in my secondary, so I don't think it could be included in other associated studies.

I will talk with you further as I look at the proposal in more detail -

Susan

Hi Susan,
Hope things are going well for you. Attached is a concept proposal for a study that I and a 3rd year fellow who I have been mentoring would like to propose as a secondary to your MRI secondary to SUPPORT.As you will see, it was originally written to include all babies with Grade 4 IVH followed by GDB. However, Rose suggested that it be proposed as a secondary to your MRI study since those ultrasounds are already being copied and read and the babies are being followed. The proposal does not presently include comparison of prediction of outcome by the detailed analysis of early head US versus discharge MRI, but if it is going to be a secondary to your study, we will include that research question as well. If numbers in SUPPORT are too small, some of the babies could be enrolled via a secondary to SUPPORT, others through the GDB follow-up study and then the rest who have GDB data could be followed as an addtional cohort. It may get complicated. Obviously, the best shot at getting the Network to fund the study is to concentrate on those babies who are presenly being followed anyway. As you will see, the budget cannot really be finalized until I find out what percentage of the babies would likely be enrolled in GDB follow-up (< or equal to 26 weeks) or SUPPORT +/- the MRI secondary). I got the total numbers of Grade 4 IVH in 2006 from the GDB book, but I can't tell how many of these are older than 26 weeks and not in SUPPORT. I also don't know how many of the SUPPORT babies with actually have Grade 4 IVH and of those, how many have gotten MRI's. So, I need to know a couple of things from you. First, what do you think of the proposal and would you consider it as a secondary to your MRI secondary? (Does that make it a tertiary study??) Second, do you know what percentage of babies in SUPPORT are getting enrolled in the MRI study? And, third, do you have any idea how many babies who have gotten MRI's so far have Grade 4 IVH? Maybe you could look through the study proposal and then we could talk on the phone. THanks very much. The fellow involved just got an abstract accepted (as a platform) on the data collected from a couple of centers in North Carolina concerning laterality of bleeds. The more extensive reading of the early head ultrasounds from this cohort is available yet.
Ricki

Ricki F. Goldstein MD
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fax: 919-681-4836

(See attached file: IVH NICHD proposal.doc)
Attachment converted: Macintosh HD:IVH NICHD proposal.doc (WDBN/«IC») (00CF9173)

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT Missing Outcomes
Date: Thursday, February 21, 2008 3:19:56 PM
Attachments: Infants with missing outcomes 02-21-08.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age.
11		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
18		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but exam entered does not meet criteria for final ROP status.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.
19		Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
22		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
23		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

24	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.
25		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

From: Zaterka-Baxter, Kristin
To: nxs5@cwru.edu; Nancy.Miller@UTSouthwestern.edu; melissa.leps@utsouthwestern.edu; ae5357@wayne.edu; du2744@wayne.edu; ellen_hale@oz.ped.emory.edu; grisbyca@email.uc.edu; ldw@iupui.edu; monica.konstantino@yale.edu; ahensman@wihri.org; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Georgia.E.McDavid@uth.tmc.edu; foy00004@mc.duke.edu; bmackinnon@tufts-nemc.org; karen-johnson@uiowa.edu; karen.osborne@hsc.utah.edu; CBackstrom@salud.unm.edu
Cc: Gantz, Marie; Das, Abhik; nfiner@ucsd.edu; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Protocol Deviation Reports
Date: Tuesday, February 19, 2008 4:05:52 PM

Hi all,
Please note we have posted a Support trial protocol deviation report for events that have not been reported on SUPP06 and separate reports that show use of HFNC in the CPAP group in the first 14 days to the NRN website (neonatal.rti.org >private gateway >administration >site reports > *your site* >support protocol deviation report.

We realize that HFNC use in the CPAP group in the first 14 days is not a protocol deviation, rather its use is discouraged; however we are monitoring HFNC in these infants because the DSMC was concerned of its seemingly high use.

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

Kris Zaterka-Baxter
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Federal Express/UPS/DHL Shipping Address:
4426 South Miami Blvd
Durham, NC 27703 USA

From: Finer, Neil
To: Michael OReilly
Cc: Joe Kiani; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade; Edmund Hey; Maribeth Savre
Subject: RE: Masimo moasked oximeters
Date: Tuesday, February 19, 2008 3:40:04 PM

Hello Michael
As I haven't received a reply as yet, I am wondering whether you have been able to answer these questions.
Many thanks
Neil Finer

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Finer, Neil
Sent: Saturday, February 09, 2008 7:29 PM
To: Michael OReilly
Cc: Joe Kiani; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade; Edmund Hey
Subject: RE: Masimo moasked oximeters

Hello Michael
Thank you for writing to me.
We need to know exactly how the firmware works - that is , will data obtained on an infant on Jan 1 2008, be
1 - available?
2 - Will it be a complete file but under Jan 2? And will the actual clock hours be correct, but labeled a day later?
3 - What will happen on March 1 or thereabouts.
As you may know, we are collecting the actual patient data as downloads off the port of the oximeters, and this data is utilized to determine the infants actual SpO2 every minute of the day that the infant is on opxygen. We match the actual times with the information about the infants inspired oxygen level, and we need to link these using the actual time.
All of the investigators world wide need these answers as soon as possible. I look forward to your response
Thanks again for getting in touch.
Hi Joe, Thanks for staying tuned
Regards
Neil Finer

-----Original Message-----
From: Michael OReilly [mailto:MOReilly@masimo.com]
Sent: Saturday, February 09, 2008 7:00 PM

To: Finer, Neil
Cc: Joe Kiani
Subject: FW: Masimo moasked oximeters

Dr. Finer,

I am the newly hired EVP of Medical Affairs for Masimo. I received this email trail as a heads up and on behalf of the company, I'm sorry for the aggravation. We are working internally to assure we communicate hardware and software changes to investigators.

Please contact me directly for any additional concerns. We continually strive to improve customer and collaborator satisfaction and appreciate your feedback.

I hope our paths cross soon.

Michael

----- Original Message -----
From: Finer, Neil <nfiner@pedsmail.ucsd.edu>
To: Maribeth Sayre; shey@easynet.co.uk <shey@easynet.co.uk>; Rich, Wade <wrich@ucsd.edu>
Cc: Chris Novak; Mike Petterson; Daniel Draper; Valerie Begnoche; Walt Weber; Ammar Al-Ali; williamtm@med.usyd.edu.au <williamtm@med.usyd.edu.au>; alpana.ghadge@ctc.usyd.edu.au <alpana.ghadge@ctc.usyd.edu.au>; Rikki Mills; Jim Litchfield; brian.darlow@chmeds.ac.nz <brian.darlow@chmeds.ac.nz>; jan@promedtech.co.nz <jan@promedtech.co.nz>; barbara.schmidt@uphs.upenn.edu <barbara.schmidt@uphs.upenn.edu>; costan@mcmaster.ca <costan@mcmaster.ca>; Stacey Taggart; Paul Cornick; Breidge Boyle <Breidge.Boyle@npeu.ox.ac.uk>
Sent: Fri Feb 08 12:32:46 2008
Subject: RE: Masimo moasked oximeters

Hello Marybeth

I am concerned regarding the tone of your email. If Masimo made a change in the firmware and was aware as you should be, that we and others are conducting research during which we are using the actual download which is keyed to the infants care on the day, hour and minute in question, we would have expected that Masimo would have informed all the users both for clinical use and research that as of Jan 1 2008, there would be a misalignment of the stored oximetry data. .As you are aware, we are using the old firmware because the new generation of firmware made changes to the serial data output stream, also never communicated to us, which would have made our data analysis software obsolete. Masimo did not inform any of us at that time, nor have they informed us about this potentially very significant issue. Masimo has created a very problematic situation regarding the interpretation of the data. It is surprising that you are upset that the users want to fix this issue as quickly and efficiently as possible, as Masimo as noted, did not inform the current users of oximeters with the old firmware of these circumstances. Wade actually called your cell to inform you of this problem.

I would hope that any future communications will be appropriate and respectful of everyone's position, and be mindful that we are using these oximeters on a large population of fragile infants to determine the optimal SpO2 ranges for their care.

Lets also set the record straight that everyone working on these studies is also very busy, mostly caring for fragile and compromised infants.

Respectfully
Neil Finer

From: Maribeth Sayre [mailto:msayre@masimo.com]
Sent: Friday, February 08, 2008 11:26 AM
To: shey@easynet.co.uk; Rich, Wade; Finer, Neil
Cc: Chris Novak; Mike Petterson; Daniel Draper; Valerie Begnoche; Walt Weber; Ammar Al-Ali; williamtm@med.usyd.edu.au; alpana.ghadge@ctc.usyd.edu.au; Rikki Mills; Jim Litchfield; brian.darlow@chmeds.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; costan@mcmaster.ca; Stacey Taggart; Paul Cornick; Breidge Boyle
Subject: Masimo moasked oximeters

Hi Gentlemen:

I must again insist that when you have problems or questions relating to the masked oximeters used in the NeoPROM trials that you notify me as the liaison person at Masimo. PLEASE DO NOT SEND QUERIES OR PROBLEMS TO WALT WEBER OR ANY OTHER OF THE ENGINEERS! By all means, send technical problems to Tech Support, and copy me, or vice versa. If there is a problem needing the expertise of any of our engineers, I, or Tech Support, will direct it to them. There are 2 reasons for this policy:
(1) As liasion person for Masimo, I need to be aware of any problems.
(2) Our engineers are extremely busy working on other projects, and we do not want them side-tracked. I hope it will not be necessary for Masimo to take steps to block your messages to engineers.

To the current problem of data labeled January 1 being repetetive, and the actual data for January 1 being the data listed for January 2: This is apparently related to 2008 being a Leap Year.

I am trying to ascertain the options for correcting the date on the data collected after Jan 1.
I will send out an email to all the NewPROM participants as soon as I have options to offer.

I will include what to expect on February 29.

I apologize for this inconvenience and will get some options to you as soon as possible.

Thanks,
Maribeth

****

From: Ricki F Goldstein
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CONCEPTS
Date: Tuesday, February 19, 2008 11:12:18 AM

Rose,
I have (b) (6) at Duke on that Monday, so, if possible, can I plan to present the concept on Tuesday, April 15th? Thanks.
Ricki

Ricki F. Goldstein MD
Associate Professor of Pediatrics
Director, High-Risk Infant Follow-up Program and
Special Infant Care Clinic
Division of Neonatology
Box 3179, Duke University Medical Center
Durham, NC 27710
office: 919-681-6024
pager: 919-970-5736
fax: 919-681-4836

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

02/19/2008 10:05 AM

To "Ricki F Goldstein" <golds005@mc.duke.edu>
cc
Subject RE: CONCEPTS

Ricki
I will save a slot for the April meeting - I need the concept (2-5 pages) by March 24.
As far as predicting or not predicting approval - I have this insight to offer: Many of the observational studies (that this would fall under) over the last few years have been sent back to the investigators with a request for a potential interventional study that will result from the observational study. The strictly observational studies (unless a secondary to a main trial, thus reducing costs) have not fared as well as studies with an intervention that could make a difference in care when the study is finished.
For costs, the coordinators would need to consent the patients for central reading of head US as well as getting them from radiology and sending them to RTI. For head US and retrieval ONLY, for the preemie iNO study, we paid for 5 coordinator hours (not including consent time - at least 2 hours to consent given that not everyone will say yes). Consent could be added to GDB at the two sites currently getting consent, but the other 14 sites would need to have compensation for consent.

The central reader would have to be budgeted for - depending how many we have, they could be done in a 2-5 day session as was done for preemie iNO or on a continuing basis when the DCC gets the scans. I assume you will want all the scans form children with grade IV's, right?

In addition, if you go outside of the "GDB" patients to get children with grade IV bleeds, they will require GDB forms so we have clinical data (3 hours/patient + time to consent these patients) as well as follow up costs. Any patients in an observational study gets $600 for FU currently. There also may be a need for tracking costs.

Congratulations to Natalie!!! Where will she be working once she completes her fellowship at UNC??

Regards,
Rose
-----Original Message-----
From: Ricki F Goldstein [mailto:golds005@mc.duke.edu]
Sent: Wednesday, February 13, 2008 4:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: CONCEPTS

I have spoken to Susan and at first glance she really doesn't think that there will be enough kids enrolled in support with Grade 4 IVH to rely on.
She thinks it would be better done on GDB kids with Grade 4 IVH. We are going to talk more on the phone. Ron may have misunderstood you or I misunderstood him, but I thought he said that you felt it would not get approved as a free standing proposal. Sorry for the misunderstanding.
Anyway, please keep my spot available to present this concept in April. Perhaps I will need to propose it as a prospective study starting with the
kids whose IVH was reported on the new data sheet starting in 2006 that captures laterality of the bleed. The budget would then involve the cost of
copying the head ultrasounds, having a central reader do the detailed reading (extent, size, location, etc) and following the additional babies
with Grade 4 IVH not already being followed in the GDB follow-up. Do you think that would have a chance of being approved?
By the way, Natalie's preliminary work has gotten accepted for both a platform presentation and poster at the SPR so we have additional preliminary info to put into the proposal. Thanks.
Ricki

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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

To: <golds005@mc.duke.edu>

cc:

Subject: 02/12/2008 05:38 PM Re: CONCEPTS

I suggested speaking with Susan Hintz. I told Ron that power may be an issue depending on the number enrolled in this secondary study.
If the secondary study does not have enough children with grade 4 IVH, it
may not be feasible as a secondary to the secondary.

Have you talked with Susan? I has suggested this previously, but don't know if you spoke with her.

Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Ricki F Goldstein <golds005@mc.duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Feb 12 17:05:26 2008
Subject: Re: CONCEPTS

Ron told me that you suggested proposing the grade 4 IVH study as a secondary to Susan's MRI secondary rather than a new concept so I was no longer planning to come to the meeting. I just spoke to Natalie Maitre today who is revising it based on some of our preliminary data accepted for
presentation at the SPR. I will send the proposal to you and Susan soon.
Ricki

Ricki F. Goldstein MD
Associate Professor of Pediatrics

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"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

02/12/2008 02:51 PM
To
"Brenda Poindexter" <bpoindex@iupui.edu>, "Ziegler, Ekhard" <ekhard-ziegler@uiowa.edu>, "Colaizy, Tarah T" <tarah-colaizy@uiowa.edu>, <golds005@mc.duke.edu>
cc
"Cunningham, Meg" <mcunningham@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Ed Bell" <Edward-bell@uiowa.edu>, "Ronald GOldberg" <goldb008@mc.duke.edu>
Subject
CONCEPTS

Hi,
I have all of you listed as presenting concepts at the upcoming Steering Committee meeting scheduled for April 14-15, 2008 at the Bolger Center in
Potomac, MD. The title is due 4-5 weeks in advance of the meeting (by March 17) and the 2-5 page concept is due by March 24. See the attached instructions for the concepts. If you concept is not received by March 24,
your allocated time may be forfeited if we have more concepts that time allows.
Let me know if there are any questions.

Thanks Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>
[attachment "Protocol%20Policy%20Changes.pdf" deleted by Ricki F Goldstein/Pediatrics/mc/Duke]

From: Janet Morgan
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Roy Heyne
Subject: Re: SUPPORT OUTCOMES
Date: Monday, February 11, 2008 7:19:47 PM

I am not sure about the eye exam . but am sure the right person will get on this. The other two (twins) that were do for 18 month have seen been relocaated and info will be entered upon my return .
Janet

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/04/08 12:25 PM >>>
Hi,

We are missing a few SUPPORT outcomes. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Finer, Neil
Subject: RE: Masimo moasked oximeters
Date: Friday, February 08, 2008 7:32:32 PM

Maribeth said she would get back to us all with an answer. I think we need to give her a couple of work days to do that before we tighten the screws.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 08, 2008 4:03 PM
To: wcarlo@peds.uab.edu; Finer, Neil
Cc: Rich, Wade
Subject: Re: Masimo moasked oximeters

Neil and Wally
Should I ask for specific study clarification from Massimo onbehalf of the NICHD Network?
Let me know - I can draft an inquiry.
Thanks for your help!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Finer, Neil <nfiner@pedsmail.ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Fri Feb 08 18:11:51 2008
Subject: RE: Masimo moasked oximeters

I agree.

wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

619 South 20th Street

525 New Hillman Building

Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: 205 266 (b) (6)

From: Finer, Neil [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Friday, February 08, 2008 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Rich, Wade
Subject: RE: Masimo moasked oximeters

Wally and Rose

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I suspect that this and we should go up Masimo's ladder and talk with their CEO. Joe Kiani.

For now, I would give them a few days to make a complete response.

I will ask that Wade fully inquire with the specific questions to them.

Be well

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 08, 2008 1:10 PM
To: Finer, Neil; Wally Carlo, M.D.
Subject: RE: Masimo moasked oximeters

This will affect all children with downloads on January 1, 2008 – many of these cases have likely had their data transferred to RTI already. Shall we see what she says first?
Thanks

Rose

From: Finer, Neil [mailto:nfiner@pedsmail.ucsd.edu]
Sent: Friday, February 08, 2008 3:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: FW: Masimo moasked oximeters

Hi Rose and Wally

I have tried to spare you some of this – but I think that the Network needs to know that there will be some issues with data alignment as a result of Masimo's firmware as of the Jan 1 date 2008.

Today there was a hailstorm of email to and from Masimo culminating in Marybeth's rather scathing response which is, quite frankly, absurd as they are the problem.

This all began from the UK starting took at data files.

We will need to discuss with RTI and develop a fix ie line up the days as they should be.

Be well

Neil

From: Finer, Neil
Sent: Friday, February 08, 2008 12:33 PM
To: 'Maribeth Sayre'; shey@easynet.co.uk; Rich, Wade
Cc: Chris Novak; Mike Petterson; Daniel Draper; Valerie Begnoche; Walt Weber; Ammar Al-Ali; williamtm@med.usyd.edu.au; alpana.ghadge@ctc.usyd.edu.au; Rikki Mills; Jim Litchfield; brian.darlow@chmeds.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; costan@mcmaster.ca; Stacey Taggart; Paul Cornick; Breidge Boyle
Subject: RE: Masimo moasked oximeters

Hello Marybeth

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I would hope that any future communications will be appropriate and respectful of everyone's position, and be mindful that we are using these oximeters on a large population of fragile infants to determine the optimal SpO2 ranges for their care.

Lets also set the record straight that everyone working on these studies is also very busy, mostly caring for fragile

and compromised infants.

Respectfully
Neil Finer

From: Maribeth Sayre [mailto:msayre@masimo.com]
Sent: Friday, February 08, 2008 11:26 AM
To: shey@easynet.co.uk; Rich, Wade; Finer, Neil
Cc: Chris Novak; Mike Petterson; Daniel Draper; Valerie Begnoche; Walt Weber; Ammar Al-Ali; williamtm@med.usyd.edu.au; alpana.ghadge@ctc.usyd.edu.au; Rikki Mills; Jim Litchfield; brian.darlow@chmeds.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; costan@mcmaster.ca; Stacey Taggart; Paul Cornick; Breidge Boyle
Subject: Masimo moasked oximeters

Hi Gentlemen:

I must again insist that when you have problems or questions relating to the masked oximeters used in the NeoPROM trials that you notify me as the liaison person at Masimo. PLEASE DO NOT SEND QUERIES OR PROBLEMS TO WALT WEBER OR ANY OTHER OF THE ENGINEERS! By all means, send technical problems to Tech Support, and copy me, or vice versa. If there is a problem needing the expertise of any of our engineers, I, or Tech Support, will direct it to them. There are 2 reasons for this policy: (1) As liasion person for Masimo, I need to be aware of any problems. (2) Our engineers are extremely busy working on other projects, and we do not want them side-tracked. I hope it will not be necessary for Masimo to take steps to block your messages to engineers.

To the current problem of data labeled January 1 being repetetive, and the actual data for January 1 being the data listed for January 2: This is apparently related to 2008 being a Leap Year.

I am trying to ascertain the options for correcting the date on the data collected after Jan 1.
I will send out an email to all the NewPROM participants as soon as I have options to offer.
I will include what to expect on February 29.

I apologize for this inconvenience and will get some options to you as soon as possible.

Thanks,
Maribeth

****

reason to believe you are not the intended recipient of this e-mail, please notify us immediately by e-mail to postmaster@masimo.com, delete all copies of this e-mail from computer memory or storage and return all hard-copies via regular mail to Masimo, 40 Parker, Irvine, California, U.S.A. 92618. Thank you.

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@pedsmail.ucsd.edu
Cc: wrich@ucsd.edu
Subject: RE: Masimo moasked oximeters
Date: Friday, February 08, 2008 10:15:15 PM

I would wait to have her give us a response; if inadequate, a letter on behalf of the NIH would be the best.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 (b) (6)

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Sent: Friday, February 08, 2008 6:03 PM
To: Wally Carlo, M.D.; nfiner@pedsmail.ucsd.edu
Cc: wrich@ucsd.edu
Subject: Re: Masimo moasked oximeters

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Cc: Rich, Wade <wrich@ucsd.edu>
Sent: Fri Feb 08 18:11:51 2008
Subject: RE: Masimo moasked oximeters

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We will need to discuss with RTI and develop a fix ie line up the days as they should be.

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Thanks,
Maribeth

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From: Wally Carlo, M.D.
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Masimo moasked oximeters
Date: Friday, February 08, 2008 4:10:51 PM

Hi Neil and Rose:

At least, the problem seems to be limited to Jan 1.

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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To: shey@easynet.co.uk; Rich, Wade; Finer, Neil
Cc: Chris Novak; Mike Petterson; Daniel Draper; Valerie Begnoche; Walt Weber; Ammar Al-Ali; williamtm@med.usyd.edu.au; alpana.ghadge@ctc.usyd.edu.au; Rikki Mills; Jim Litchfield; brian.darlow@chmeds.ac.nz; jan@promedtech.co.nz; barbara.schmidt@uphs.upenn.edu; costan@mcmaster.ca; Stacey Taggart; Paul Cornick; Breidge Boyle
Subject: Masimo moasked oximeters

Hi Gentlemen:

I must again insist that when you have problems or questions relating to the masked oximeters used in the NeoPROM trials that you notify me as the liaison person at Masimo. PLEASE DO NOT SEND QUERIES OR PROBLEMS TO WALT WEBER OR ANY OTHER OF THE ENGINEERS! By all means, send technical problems to Tech Support, and copy me, or vice versa. If there is a problem needing the expertise of any of our engineers, I, or Tech Support, will direct it to them. There are 2 reasons for this policy: (1) As liasion person for Masimo, I need to be aware of any problems. (2) Our engineers are extremely busy working on other projects, and we do not want them side-tracked. I hope it will not be necessary for Masimo to take steps to block your messages to engineers.

To the current problem of data labeled January 1 being repetetive, and the actual data for January 1 being the data listed for January 2: This is apparently related to 2008 being a Leap Year.

I am trying to ascertain the options for correcting the date on the data collected after Jan 1.
I will send out an email to all the NewPROM participants as soon as I have options to offer.
I will include what to expect on February 29.

I apologize for this inconvenience and will get some options to you as soon as possible.

Thanks,
Maribeth

****

CONFIDENTIALITY NOTICE

From: Angelita Hensman
To: Abbot Laptook; Gantz, Marie; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; adas@rti.org; Pickett, James; Auman, Jeanette O.; Cunningham, Meg; Huitema, Carolyn Petrie; Yost, Patricia A.
Subject: RE: Pulse Oximeter Gap Resolution
Date: Friday, February 08, 2008 10:28:03 AM

I checked our site report on the 1 infant (DOB (b) (6) . As far as I can tell an extraction was done on (b) (6) and transmitted to RTI. We are missing data from (b) (6) (21 days) and (b) (6) (24 day) . This was at the time downloads were to be done **every 30 days per protocol** . We switched to every two week downloads because we were told the data was being written over although I cannot find a memo on the the date we switched. Maybe RTI knows. It seems like this is was what happened with this baby and we have no way to retrieve that information.

Angelita

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, February 05, 2008 2:17 PM
To: nxs5@cwru.edu; Nancy.Miller@UTSouthwestern.edu; melissa.leps@utsouthwestern.edu; ae5357@wayne.edu; du2744@wayne.edu; ellen_hale@oz.ped.emory.edu; grisbyca@email.uc.edu; ldw@iupui.edu; monica.konstantino@yale.edu; Angelita Hensman; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Georgia.E.McDavid@uth.tmc.edu; foy00004@mc.duke.edu; bmackinnon@tufts-nemc.org; karen.osborne@hsc.utah.edu; CBackstrom@salud.unm.edu; Rich, Wade; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; karen-johnson@uiowa.edu; [SCRN] Stoll, Barbara; kurt.schibler@cchmc.org; bpoindex@iupui.edu; richard.ehrenkranz@yale.edu; Abbot Laptook; vanmeurs@stanford.edu; wcarlo@peds.uab.edu; Kathleen.A.Kennedy@uth.tmc.edu; goldb008@mc.duke.edu; IFrantz@tufts-nemc.org; edward-bell@uiowa.edu; Roger.Faix@hsc.utah.edu; kwatterberg@salud.unm.edu; bradley.yoder@hsc.utah.edu; Brenda.H.Morris@uth.tmc.edu; susie.buchter@oz.ped.emory.edu; Michael Cotten
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie; Pickett, James; Auman, Jeanette O.; Cunningham, Meg; Huitema, Carolyn Petrie; Yost, Patricia A.
Subject: Pulse Oximeter Gap Resolution

Hello all,

RTI has created reports of gaps in SUPPORT pulse oximeter data of 15 days or longer. Gaps have been verified as time on support using forms SUPP05 and SUPP11, and gaps already reported as protocol deviations on form SUPP06 are not included. Please review your center's report and take the following steps to help resolve these gaps.

Report Location: www.neonatal.rti.org /Private Gateway/Administration/Site Reports/Support Pulse Ox Gap Reports.
Please note; if there have been no gaps in pulse-ox data of 15 days or longer identified at your site, the report title will have the additional text "No Data Available".

1) Some gaps overlap with pulse oximeter extraction dates recorded by the center in the transmission log. If this is the case, the numbers and dates of overlapping extractions are listed in the report. Please retransmit the extractions listed to RTI in case they did not transmit properly the first time.
2) If a gap has no overlapping extractions listed, please check to see if you have extractions that were never sent to RTI. If so, please transmit those files. If not, please let us know if there is a reason why the infant has no pulse oximeter data for the dates of the gap.
3) A few centers have additional requests to retransmit extractions that were previously sent to RTI but were corrupted. If you have such a request on your report, please retransmit the extractions listed.

If you have questions about the gap reports, please contact Marie Gantz at 828-254-6255 or mgantz@rti.org. If you have questions regarding the transmission of extractions, please contact James Pickett at 919-541-1253 or japickett@rti.org.

Thanks,
Kris

Kris Zaterka-Baxter
Statistics and Epidemiology Division
RTI International
3040 Cornwallis Road
P.O. Box 12194
RTP, NC 27709-2194 USA
(tel) 919-485-7750
(fax) 919.485.7762
kzaterka@rti.org
www.rti.org

Federal Express/UPS/DHL Shipping Address:
4426 South Miami Blvd
Durham, NC 27703 USA

From: Gantz, Marie
To: KWatterberg@salud.unm.edu
Cc: Zaterka-Baxter, Kristin; Pickett, James; Higgins, Rosemary (NIH/NICHD) [E]; jrohr@salud.unm.edu
Subject: RE: Pulse Oximeter Gap Resolution
Date: Thursday, February 07, 2008 4:42:20 PM

Hi Kristi,

We are tracking corruptions and gaps of all sizes in the pulse oximeter data. Our strategy for resolving the gaps is to work on the larger (15+ days) gaps and known corruptions before tackling the smaller gaps. If the extractions noted on your gap report could be retransmitted that would help us in case we did not receive of the data in the files the first time. Thanks very much for helping us with this process. If you have questions about re-transmitting the data please contact James Pickett directly.

Marie

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

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Thursday, February 07, 2008 3:21 PM
To: Zaterka-Baxter, Kristin
Cc: Rosemary (NIH/NICHD) Higgins; Julie Rohr
Subject: Re: Pulse Oximeter Gap Resolution

Hi, Kris. Julie looked into the 3 gaps for NM - all three had been previously sent, and confirmed as received at RTI. We can re-send these, but Julie is concerned that there could be problems of shorter duration or other corruptions on other sent downloads that we are unaware of. Are you tracking this? thanks, Kristi

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 2/5/2008 12:16 PM >>>
Hello all,

RTI has created reports of gaps in SUPPORT pulse oximeter data of 15 days or longer. Gaps have been verified as time on support using forms SUPP05 and SUPP11, and gaps already reported as protocol deviations on form SUPP06 are not included. Please review your center's report and take the following steps to help resolve these gaps.

Report Location: www.neonatal.rti.org /Private Gateway/Administration/Site Reports/Support Pulse Ox Gap Reports.
Please note; if there have been no gaps in pulse-ox data of 15 days or longer identified at your site, the report title will have the additional text "No Data Available".

1) Some gaps overlap with pulse oximeter extraction dates recorded by the center in the transmission log. If this is the case, the numbers and dates of overlapping extractions are listed in the report. Please retransmit the extractions listed to RTI in case they did not transmit properly the first time.
2) If a gap has no overlapping extractions listed, please check to see if you have extractions that were never sent to RTI. If so, please transmit those files. If not, please let us know if there is a reason why the infant has no pulse oximeter data for the dates of the gap.
3) A few centers have additional requests to retransmit extractions that were previously sent to RTI

but were corrupted. If you have such a request on your report, please retransmit the extractions listed.

If you have questions about the gap reports, please contact Marie Gantz at 828-254-6255 or mgantz@rti.org. If you have questions regarding the transmission of extractions, please contact James Pickett at 919-541-1253 or japickett@rti.org.

Thanks,
Kris

Kris Zaterka-Baxter
Statistics and Epidemiology Division
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4426 South Miami Blvd
Durham, NC 27703 USA

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich
Subject: Re: SUPPORT OUTCOMES
Date: Thursday, February 07, 2008 12:01:51 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> We are missing a few SUPPORT outcomes. Please let us know how you are doing.
>
> Thanks for all the effort!!
> Rose

CENTER	NETWORK	ROP_message
13	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

H Rose,
We have been trying to reach both babies. One of those babies was transferred to another hospital and then discharged in July with 2 negative ROP eye exam, he only needs one more exam to reach status. We have been trying unsuccessfully to get in touch with the mom to see if she has made the followup eye appointment. The second baby had an outpatient eye exam scheduled but the baby was readmitted with meningitis, she is home now and we have been trying to reach her as well. We may have better luck with her as the baby is seen here in our premieclinic. We will keep trying! thanks,
Monica

From: Elizabeth Billian
To: Higgins, Rosemary (NIH/NICHD) [E]; Beena Sood; Seetha Shankaran
Cc: Becky Bara
Subject: SUPPORT Outcomes
Date: Wednesday, February 06, 2008 10:43:17 AM

Here is the update on the ROP outcomes:

(b) (6) Infant was 72 weeks on (b) (6) Her last eye exam was 10/12/07 (zone 3, stage 0) and she was next scheduled for 2/1/08 but she was re-scheduled for 2/15/08. Will follow up on that exam.

(b) (6) Recently, the ROP form was coded "Y" to Lost to follow up at 55 weeks PMA. This infant was 74 weeks on (b) (6) her last exam was 9/24/07 (zone-undetermined and stage 0). She was rescheduled several times but was a no show; her last appointment was on 1/10/08. Her mother can not be reached by phone; in the past, she was informed of the importance of continued eye exams. A letter will be sent to her current address.

(b) (6) This infant was seen on 1/4/08 and his final status was zone 4. The data was entered on 2/5/08.

(b) (6) This infant was seen on 1/4/08 and his final status was zone 4. The data was entered on 2/5/08.

Question re (b) (6) The NG03 and NG07 data were entered on 1/23/08.

If questions- please contact me. Thanks

Betty Billian

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OUTCOMES
Date: Tuesday, February 05, 2008 6:15:40 PM

NF05 was completed in March of 2007 according to my computer.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 05, 2008 7:43 AM
To: Finer, Neil; Rich, Wade; Vaucher, Yvonne; Fuller, Martha
Cc: Gantz, Marie; Adas@rti.org
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.
Given your recruitment, this is outstanding!!!
Thanks for all the effort!!
Rose

CENTER	NETWORK	FU_message
22	(b) (6)	FU window has closed but NF05 has not been completed

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Katherine A Foy
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org; cotte010@mc.duke.edu; goldb008@mc.duke.edu; golds005@mc.duke.edu; lohme001@mc.duke.edu; mgantz@rti.org
Subject: Re: SUPPORT OUTCOMES
Date: Tuesday, February 05, 2008 9:09:47 AM

I have gone through several of the 50 weeks PMA and have entered them into the computer. The others I am still trying to get some ROP exam on. Melody and I talked about the kids in the FU group and she is still trying to get those kids back to clinic. I will keep working on these kids and get as much information into the computer that I can.
Have a great day,

Kathy Foy
Clinical Research Coordinator
Duke University Health Systems
Neonatology
668-3360 office
970(b) (6) pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
02/04/2008 02:10 PM

To: <foy00004@mc.duke.edu>
cc: <adas@rti.org>, <cotte010@mc.duke.edu>, <goldb008@mc.duke.edu>, <golds005@mc.duke.edu>, <lohme001@mc.duke.edu>, <mgantz@rti.org>
Subject: Re: SUPPORT OUTCOMES

Thanks!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Katherine A Foy <foy00004@mc.duke.edu>

To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org <adas@rti.org>; Michael Cotten <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Ricki F Goldstein <golds005@mc.duke.edu>; lohme001@mc.duke.edu <lohme001@mc.duke.edu>; Gantz, Marie <mgantz@rti.org>
Sent: Mon Feb 04 14:12:07 2008
Subject: Re: SUPPORT OUTCOMES

I am working on them as we speak. I will get in touch with Melody to see if there are any changes in the fu.

Kathy Foy
Clinical Research Coordinator
Duke University Health Systems
Neonatology
668-3360 office
970(b) (6) pager

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
02/04/2008 02:03 PM

To: <goldb008@mc.duke.edu>, "Ricki F Goldstein" <golds005@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, <lohme001@mc.duke.edu>, <foy00004@mc.duke.edu>
cc: <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER NETWORK ROP_message

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.

19 (b) (6) Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

19 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

19 (b) (6) No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

CENTER NETWORK BPD_message

19 (b) (6) PHY01 is expected based on NG07 but has not been entered

CENTER NETWORK FU_message

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

19 (b) (6) FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Wilson, Leslie Dawn
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B
Cc: adas@rti.org; Gantz, Marie; Hamer, Faithe Angeline
Subject: RE: SUPPORT OUTCOMES
Date: Tuesday, February 05, 2008 8:43:23 AM

Hi.

Pt (b) (6) -Second zone 3 was entered in January.
Pt (b) (6) -Pt has not shown up for last few visits, still waiting for final visit.

Kind Regards-leslie

Leslie Dawn Wilson, RN, BSN
Research Manager
Neonatal Network Coordinator
Riley Hospital RR 208
ldw@iupui.edu (e-mail)
699 West Dr
Indianapolis, IN 46202
317.274.8255 (phone)
317.274.8963 (fax)
317.312.(b) (6) (pager)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 04, 2008 1:44 PM
To: Poindexter, Brenda B; Wilson, Leslie Dawn
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
12	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Phelps, Dale; Everett-Thomas, Ruth; Hobson, Laverne; Bauer, Charles R; Auman, Jeanette O.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT OUTCOMES
Date: Monday, February 04, 2008 4:28:18 PM
Attachments: Missing ROP outcomes for SUPPORT.msg

Shahnaz,

To reiterate what it says in the attached email from November, it was determined through conversations between RTI and Dale Phelps that it made the most sense to let you mark the ROP outcomes as permanently missing using the new questions on SUPP10. These questions should now be available to you in the DMS. Once the SUPP10 reflects the fact that the ROP outcomes for these four infants are permanently missing, they will no longer appear on the monthly missing data reminders. If you have any problems entering the data into the DMS, Jenny Auman can help you resolve them.

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
919-541-6956

From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Monday, February 04, 2008 2:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Phelps, Dale; Gantz, Marie; Everett-Thomas, Ruth; Hobson, Laverne; Bauer, Charles R
Subject: RE: SUPPORT OUTCOMES

Rose,

I believe that the final ROP status on these babies was limited to finding a way to record the fact that they were never seen in ROP clinic at any time – we were unable to find any documentation of a follow up appointment when charts were reviewed at the time of developmental follow up. Dale, Ruth and I communicated over this issue late Nov and I thought the matter was closed. Has something new come up?

The follow up queries are new – we will move on those right away.

Thanks
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 04, 2008 1:28 PM
To: Duara, Shahnaz; Everett-Thomas, Ruth; Bauer, Charles R
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
8	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
CENTER	NETWORK	FU_message
8	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
8	[redacted]	FU window has closed but NF05 and NF09a have not been completed
8	[redacted]	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vivien Phillips
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Myriam Peralta, M.D.
Cc: adas@rti.org; Gantz, Marie
Subject: RE: SUPPORT OUTCOMES
Date: Monday, February 04, 2008 3:10:00 PM

We haven't given up on the SUPPORT 18 month follow up - #(b) (6) has been rescheduled several times and is scheduled to come on Thursday (2/7) and (b) (6) has missed earlier appts but is scheduled to come on 2/28.
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 04, 2008 12:59 PM
To: Wally Carlo, M.D.; Monica Collins; Shirley Cosby; Vivien Phillips; Myriam Peralta, M.D.
Cc: adas@rti.org; Gantz, Marie
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.

THIS IS ABSOLUTELY OUTSTANDING GIVEN YOUR INCREDIBLE RECRUITMENT!!!!!

Thanks for all the effort!!
Rose

CENTER	NETWORK	BPD_message
16	(b) (6)	Infant was not eligible for challenge (per PHY01) but NG07 36 week snapshot is not entered (Note: NG03 not yet entered)
CENTER	NETWORK	FU_message
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed
16	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT OUTCOMES
Date: Monday, February 04, 2008 2:36:28 PM

Rose,

(b) (6) is completed and will be sent with the next transmission.
(b) (6) is waiting on an opthamology visit. This baby has been hospitalized several times and has missed appointments.

As far as follow up...if it's not transmitted with this next transmission I won't be able to answer the question. Our follow-up coordinator went (b) (6) today and we don't have anyone to really take her place. She was hoping she got everything done before (b) (6). We don't expect (b) (6). I'll keep you updated if it's going to be longer than that.
Thanks,
Nancy

Nancy A. Miller, R.N.
Clinical Research Coordinator
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-404B
Dallas, Texas 75390-9063
214-648-3780
pager 972-206-(b) (6)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/4/2008 12:25 PM >>>
Hi,

We are missing a few SUPPORT outcomes. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER

NETWORK

ROP_message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

CENTER

NETWORK

FU_message

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

4

(b) (6)

FU window has closed but NF05 and NF09a have not been completed

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Bonnie Siner
To: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; "nancy newman"; drfjcmd@aol.com
Cc: "Gantz, Marie"; adas@rti.org
Subject: RE: SUPPORT OUTCOMES
Date: Monday, February 04, 2008 1:45:18 PM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 04, 2008 1:24 PM
To: mcw3@cwru.edu; nancy newman; drfjcmd@aol.com; Bonnie Siner
Cc: Gantz, Marie; adas@rti.org
Subject: SUPPORT OUTCOMES

Hi,
We are missing a few SUPPORT outcomes. Please let us know how you are doing.
Given the number of patients recruited at your site, this is OUTSTANDING!!!!!!
Thanks for all the effort!!
Rose

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Still tracking.

3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Entered and transmitted 1/23/08.

CENTER	NETWORK	FU_message
3	(b) (6)	FU window has closed but NF05 and NF09a have not been completed

Baby seen in Cincinnati

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT follow up
Date: Saturday, February 02, 2008 11:22:20 AM
Importance: High

Hi Rose

It occurs to me that maybe you should send this email to the neurodevelopmental follow-up PI's at the sites too since they are the ones that will have to implement the request - sometimes there is not the greatest communication between the site PI's and the follow-up PI's.

Thanks

Susan

> Hi,
>
> The protocol review committee reviewed the SUPPORT 6-7 year FU study submitted by Susan Hintz today. The subcommittee is requesting revisions and a re-review of the protocol prior to forwarding to the steering committee. There is significant enthusiasm for this study. In the meantime, the committee is asking that sites seeing patients in follow up who have had the neuroimaging studies done as a secondary to the SUPPORT Trial to **request permission to re-contact the family** in the event that the 6-7 year FU study goes forward.
>
> Let me know if there are any questions.
>
> Thanks
>
> Rose
>
> Rosemary D. Higgins, M.D.
>
> Program Scientist for the Neonatal Research Network
>
> Pregnancy and Perinatology Branch
>
> Center for Developmental Biology and Perinatal Medicine
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> MSC 7510
>
> Bethesda, MD 20892

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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Wally Carlo, M.D.
To:	Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc:	Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz
Subject:	RE: SUPPORT ANCILLARY STUDY
Date:	Friday, January 25, 2008 1:22:27 PM

To me it would be ideal if the primary hypothesis was related to the randomization.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 23, 2008 2:34 PM
To: nfiner@ucsd.edu; Walsh, Michele; wacarlo@uab.edu; wrich@ucsd.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Das, Abhik; Abbot Laptook; kurt.schibler@cchmc.org; nancy newman; Gantz, Marie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Susan Hintz
Subject: SUPPORT ANCILLARY STUDY

Hi
Attached is a secondary to SUPPORT for FU and potential 6-7 year FU. Let me know if you would like to have a call to discuss. I have included Susan Hintz on the email as this relates to the MRI/FU and the potential 6-7 year FU protocol.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
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Bethesda, MD 20892
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: SUPPORT missing outcomes report
Date: Friday, January 25, 2008 9:43:18 AM
Attachments: Infants with missing outcomes 01-24-08.xls

Rose,

Attached is the list of SUPPORT infants who are missing outcomes this month.

Thanks,
Marie

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

Missing_ROP

CENTER	NETWORK	ROP_message
3	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
3		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
4		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
5		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
8		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
9		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
9		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11		SUPP10 Q:'Final ROP status determined at 18M FU'=Y but infant is <18 months adjusted age
11		No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
12		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
13		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18		SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
18		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the left eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

(b) (6)

19	Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.
19	Infant died more than a week after the last ROP exam and final ROP status has not been obtained. Please confirm that all ROP exams have been entered.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
19	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
23	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
24	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed.
25	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
25	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
25	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Sunday GRP NRN proposal
Date: Wednesday, January 23, 2008 11:46:40 PM

I vote Yes
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 23, 2008 11:56 AM
To: Finer, Neil; Walsh, Michele; wacarlo@uab.edu; Bradley Yoder; Roger.Faix@hsc.utah.edu; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: Sunday GRP NRN proposal

Hi,
Attached is the concept for GRP as a secondary to SUPPORT. The steering committee approved the concept at the recent meeting. Please send a yes/no vote for subcommittee approval of the protocol by January 28. If the subcommittee approves - this will go to protocol review. The investigators have money to cover the costs of the secondary study. The network would need to support RTI costs such as development of forms and data analysis.
Thanks
Rose
<<Sunday GRP NRN proposal.doc>>

From:	Finer, Neil
To:	Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	RE: SUPPORT Meeting Minutes
Date:	Sunday, January 13, 2008 11:26:14 PM
Attachments:	SUPPORT Subcommittee Report Meeting Jan 10, 2008.ppt

Hi Everyone
I guess my true colors are showing. Sorry for sending out the wrong version of the minutes of our Jan 10 2008 meeting
Hopefully this is current and correct
Thanks Abbott for getting to me so quickly
Be well
Neil

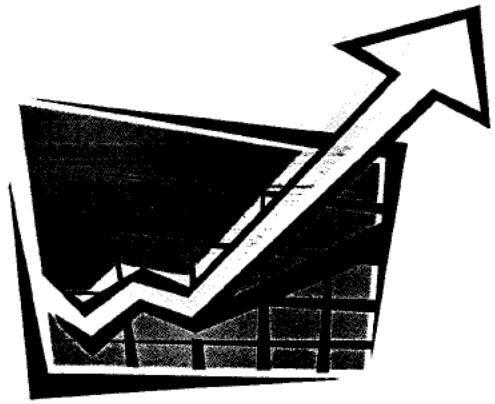
From: Finer, Neil
Sent: Friday, January 11, 2008 2:37 PM
To: Finer, Neil; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade
Subject: RE: SUPPORT Meeting Minutes

Hello Everyone
Please find the minutes of our subcommittee.
Let me know if you have any corrections and additions.
Be well
Neil

SUPPORT Subcommittee Report – January 10, 2008

Review of Enrollments to date:

- As of most current information - 884 infants enrolled representing 67% of total
- This rate has been some what improved- averaging 35 month over past 6 months
- Projection – Probably enrollment will be complete by Feb-Mar 2009



SUPPORT Subcommittee

Review of Serious Adverse Events

- All such events apart from air leaks in the first 14 days are occurring at less than the baseline rates, and the air leaks are only marginally increased for the larger strata by 0.2%.
- The incidence of compressions by decreased by half, and pulmonary hemorrhages and IVH down by 1/3 – 1/4
- These are NOT between randomized groups!!

Review Protocol Violations

Commonest:

1. **Failure to use Study Oximeter when required**
2. **Use of HiFlow NC**

- **Newer centers not using study oximeters when indicated**
- **This accounts for largest category Centers 24, 25 26 range from 19% to 38%.**
- **The next highest is 15 and 13% and all others are < 10%**

Protocol Deviations

- **At last meeting we had agreed that > 25% perhaps as a high target and target review at time of site review**
- **Center 25 uses HiFlow NC and this accounts for most of their deviations = 27% of 62%.**
- **Encourage Centers to review their experience**

Review of Oximeter Downloads

- Through Dec 07 we are 12.9% > 96%, and then 8.2% < 84%% for first 14 days and 19% and 12.6% after 14 days
- This is similar to our last period
- Continue to reinforce need to keep in SpO2 targets

MRI Secondary – S Hintz

- **Enrollment/MRI central reading update**
  - 337 patients have been enrolled
    - 35-42 week neuroimaging *including MRI* is complete for ~242 patients
      - 48 patients died before late neuroimaging
- MRI central reading: approximately 165 have been read or are in process with central reader. Fifty more sent by RTI this past week

Breathing Outcomes: Tim Stevens

Enrollment = 529 consented by Jan 1 2008, represents almost 60% of SUPPORT

From Sept to December = 73 additional patients consented

Questionnaire follow-up good - 139 infants

Breathing Outcomes

- **Two investigator groups have approached us to request use of the 4 questionnaire series and manual of procedures to assess outpatient pulmonary outcome as part of 2 RCTS**
- **Drs. Jon Davis and Richard Parad have requested to use the tool as a secondary outcome measure of their recombinant SOD Trial and Dr. Roberta Ballard has requested the tool to do the same for her TOLSURF Study (Trial of Late SURFactant).**
- **Rose Higgins has asked the Steering Committee to vote by January 18th on approval to share the questionnaires with these investigators.**

Antenatal Consent - W Rich

- 9 sites completed
- 2484 Women have been screened and 868 delivered in the study window since study began

Growth – Progressing – no report given

Will obtain a more detailed report at next Meeting

Physiologic Definition of BPD for SUPPORT

- After conference call, we decided to continue using the PHY 01, and 02 as currently written and will therefore collect the actual FiO2 and any flow using the eligibilty from the PHY 01 form for all infants
- We will have the opportunity to perform any adjustments as we decide for infants at altitude
- The GDB Subcommittee and Steering committee need to review the definition of BPD for infants at altitude

Hot Topics Presentation

- Pediatrix Administrative Database review presented demonstrated that there appeared to be an increase in NEC and PDA with introduction of lower range of SpO2 – low end = SpO2 = 83%
- There was no patient data presented, and no actual SpO2 data collected
- Subsequent communication with senior Pediatrix Officials suggested that the results may have been one center and that there was no significant relationship noted.

Hot Topics Presentation

- There was a suggestion from Dr Spong that we need to inform IRBs as this information was publicly reported.
- However there does not appear to be any significant new information relating to the use of any SpO2 range and any outcomes.
- Our committee felt that there was no indication for informing our IRBs.
- Rose will revisit this issue with Dr Spong

SUPPORT Subcommittee SUMMARY

- Study now > 67% complete
- At 35/month, last 6 month level, we will need 13 more months
- Secondaries are enrolling at reasonable rates and will be very informative
- We will probably miss PAS 2009 as we will need at least 4 months after the last enrolled infant before we can close the study and that may be optimistic!!!

SUPPORT Subcommittee SUMMARY

- **Thanks to all the Coordinators for their incredible work for this trial!!**

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Sunday, January 13, 2008 9:41:20 AM

Yes, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 9:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; Abbot Laptook; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Stevens, Timothy; Phelps, Dale
Subject: Requests to use SUPPORT Pulmonary outcomes questionnaire

Hi,
I have two requests for investigators to use the pulmonary outcomes questionnaire for studies in development. Robert Ballard requests to use this instrument in her TOLSURF Trial and Rich Parad and Jon Davis request to use this in their recombinant SOD trial. I have attached summaries from both studies. The Investigators from the Tucson Asthma study had given us permission to use and modify their questionnaire and have also granted permission for further use by these two investigative teams.

Please send me a yes/no vote by January 18.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd., Room 4B03B
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(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From:	Finer, Neil
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	RE: SUPPORT Meeting Minutes
Date:	Friday, January 11, 2008 6:16:07 PM
Attachments:	SUPPORT SubCommittee Jan 11 2007.ppt

Hi Everyone
I had the date wrong and forgot the issues around Hot Topics.
Be well
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Finer, Neil
Sent: Friday, January 11, 2008 2:37 PM
To: Finer, Neil; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade
Subject: RE: SUPPORT Meeting Minutes

Hello Everyone
Please find the minutes of our subcommittee.
Let me know if you have any corrections and additions.
Be well
Neil

SUPPORT SubCommittee Report

- Enrollments = 475
- All but one center actively enrolling
- Alabama – sets new record 15 in a month!!!
- Projection = will require 25 months with 17 centers enrolling 2 patients/month/site
- At 3/month/site we would be completed in 17 months
- UCSD now enrolling – enrolled first patient Jan 11, 2006

SUPPORT: Secondaries Breathing Outcomes

- 188 enrolled
- 75 infants at 12 month window
- All new sites doing their own follow-up
- Dr Stevens funded for K23

SUPPORT: Secondaries
MRI

- 142 enrolled
- 3 New Sites enrolling
- 3 sites not participating
- Discussion about convincing IRB to accept this study – Susan will provide data about how many babies were studied without sedation
- 3 sites do or try to do MRI as standard of care predischarge.
- In infant consented, and does not have MRI, head ultrasounds if available should be sent .

SUPPORT: Secondaries Growth and Consent

- Enrollment = 83
- Discussion about timing of measurements
- Suggestion that timing be +/- 3 days.
- Will circulate to co-ordinators and seek consensus
- Consent will require 50 enrolled patients from inception of this Secondary

SUPPORT – Other Issues

- What to do if parental consent obtained and team does not have randomization
- Act as if Baby is a CPAP infant
- If infant requires intubation for resuscitation, not a problem
- If infant intubated without indications, indicate by a protocol deviation and carry on with study

SUPPORT: Adverse Events

Occurrence lower than baseline predictions

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	5.5	8.5	3.5
Air leak	6.1	7.1	5.5
Pulmonary hemorrhage	5.2	7.1	3.9
Severe IVH (grades III-IV)	12.8	17.8	9.3

SUPPORT – Other Issues

Oximeters

- Downloads sent to sites – but need to have 5 infants and at least 1 per arm
- Encourage use of trend plots to enforce target levels
- Compliance visit – first one complete and went well

SUPPORT – Other Issues

- Thanks to everyone for all the work to date, and especially the movement of oximeters between sites.
- We are ready to help at any level including site visits
- Keep up the great work!!

From: Finer, Neil
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject: RE: SUPPORT Meeting Minutes
Date: Friday, January 11, 2008 5:46:21 PM
Attachments: SUPPORT Subcommittee Report Meeting Jan 10, 2008.ppt

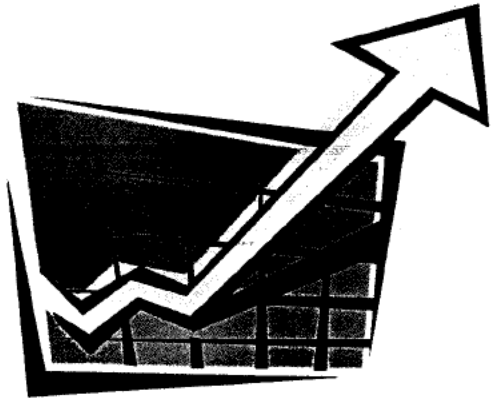
---

Hello Everyone
Please find the minutes of our subcommittee.
Let me know if you have any corrections and additions.
Be well
Neil

SUPPORT Subcommittee Report – Meeting October 15 2007

Review of Enrollments to date:

- As of most current information - 884 infants enrolled representing 67% of total
- This rate has been some what improved- averaging 35 month over past 6 months
- Projection – Probably enrollment will be complete by Feb-Mar 2009



SUPPORT Subcommittee

Review of Serious Adverse Events

- All such events apart from air leaks in the first 14 days are occurring at less than the baseline rates, and the air leaks are only marginally increased for the larger strata by 0.2%.
- The incidence of compressions by decreased by half, and pulmonary hemorrhages and IVH down by 1/3 – 1/4
- These are NOT between randomized groups!!

Review Protocol Violations

Commonest:

1. **Failure to use Study Oximeter when required**
2. **Use of HiFlow NC**

- **Newer centers not using study oximeters when indicated**
- **This accounts for largest category Centers 24, 25 26 range from 19% to 38%.**
- **The next highest is 15 and 13% and all others are < 10%**

Protocol Deviations

- **At last meeting we had agreed that > 25% perhaps as a high target and target review at time of site review**
- **Center 25 uses HiFlow NC and this accounts for most of their deviations = 27% of 62%.**
- **Encourage Centers to review their experience**

Review of Oximeter Downloads

- Through Dec 07 we are 12.9% > 96%, and then 8.2% < 84%% for first 14 days and 19% and 12.6% after 14 days
- This is similar to our last period
- Continue to reinforce need to keep in SpO2 targets

MRI Secondary – S Hintz

- **Enrollment/MRI central reading update**
  - 337 patients have been enrolled
    - 35-42 week neuroimaging *including MRI* is complete for ~242 patients
      - 48 patients died before late neuroimaging
- MRI central reading: approximately 165 have been read or are in process with central reader. Fifty more sent by RTI this past week

Breathing Outcomes: Tim Stevens

Enrollment = 529 consented by Jan 1 2008, represents almost 60% of SUPPORT

From Sept to December = 73 additional patients consented

Questionnaire follow-up good - 139 infants

Breathing Outcomes

- **Two investigator groups have approached us to request use of the 4 questionnaire series and manual of procedures to assess outpatient pulmonary outcome as part of 2 RCTS**
- **Drs. Jon Davis and Richard Parad have requested to use the tool as a secondary outcome measure of their recombinant SOD Trial and Dr. Roberta Ballard has requested the tool to do the same for her TOLSURF Study (Trial of Late SURFactant).**
- **Rose Higgins has asked the Steering Committee to vote by January 18th on approval to share the questionnaires with these investigators.**

Antenatal Consent - W Rich

- 9 sites completed
- 2484 Women have been screened and 868 delivered in the study window since study began

Growth – Progressing – no report given

Will obtain a more detailed report at next Meeting

Physiologic Definition of BPD for SUPPORT

- After conference call, we decided to continue using the PHY 01, and 02 as currently written and will therefore collect the actual FiO2 and any flow using the eligibilty from the PHY 01 form for all infants
- We will have the opportunity to perform any adjustments as we decide for infants at altitude
- The GDB Subcommittee and Steering committee need to review the definition of BPD for infants at altitude

SUPPORT Subcommittee SUMMARY

- Study now > 67% complete
- At 35/month, last 6 month level, we will need 13 more months
- Secondaries are enrolling at reasonable rates and will be very informative
- We will probably miss PAS 2009 as we will need at least 4 months after the last enrolled infant before we can close the study and that may be optimistic!!!

SUPPORT Subcommittee SUMMARY

- **Thanks to all the Coordinators for their incredible work for this trial!!**

From: Finer, Neil
To: Ronald N Goldberg
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Proposal
Date: Friday, January 11, 2008 5:53:49 PM

Hi Ron
I like the proposal.
You need to indicate how the urine is preserved and shipped?
(frozen etc)
This is very doable and could be complete by the time SUPPORT is complete.
I am very supportive.
Do you need any $$ or are does the investigator have all the required $$?
Let me know what you need from me.
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

-----Original Message-----
From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Thursday, January 10, 2008 2:29 PM
To: Finer, Neil
Subject: Fw: Proposal

Try this.

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

From: Michael Cotten
Sent: 01/10/2008 04:59 PM EST
To: Ronald Goldberg
Subject: Re: Proposal

(See attached file: Gastrin-Releasing%20Peptide%20and%20BPD%20-%20Mary%20Sunday.pdf)(See attached file: MS GRP Networkconcept.ppt)

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710

ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

Ronald N

Goldberg/Pediatri

cs/mc/Duke

To

Michael

01/10/2008 04:57 Cotten/Pediatrics/mc/Duke@mc

PM

cc

Subject

Re: Proposal(Document link:

Michael

Cotten)

Do you have the thing we sent in?
I had it but it didn't go through.
Ron

----- Original Message -----
From: Michael Cotten [cotte010@mc.duke.edu]
Sent: 01/10/2008 04:50 PM EST
To: Ronald Goldberg
Subject: Re: Proposal

you could send him the slides I made and teh concept pdf (enclosed)

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Director Neonatology Clinical Research
Duke University Medical Center
Box 3179 DUMC
Durham, NC 27710
ph: 919-681-6024
fax: 919-681-6065
email: cotte010@mc.duke.edu

Ronald N Goldberg

<goldb008@mc.duke.edu>

To
01/10/2008 04:09 PM "Neil Finer" <nfiner@ucsd.edu>,

"Mike Cotten"
<cotte010@mc.duke.edu>

cc

Subject
Re: Proposal

Sorry will try when I get back to my room.
Ron

----- Original Message -----
From: "Finer, Neil" [nfiner@ucsd.edu]
Sent: 01/10/2008 12:42 PM PST
To: Ronald Goldberg
Subject: RE: Proposal

Hi Ron
These attachments look like images - there appears to be no actual file
Neil

From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Friday, December 07, 2007 1:13 PM
To: Finer, Neil
Subject: Fw: Proposal

Dear Neil,
Hope you're well and the holidays haven't been miserable. Anniversaries are
killers.
I am looking foward to seeing you in January-can i buy you a drink?
Mary Sunday and my group would like to present the attached as a concept proposal with the hope of being a secondary to the SUPPORT study.
The potential of this GRP being a marker of increased risk of BPD(it is a
proinflammatory peptide) and the existence of an anti-GRP(NIH holds the IND) which Mary and Jacki Coalson are studying in baboons, is exciting.
Please take a look and tell me what you think and how to go foward. I've sent this to Rose.
(b) (6) (this is an impossible word to spell),
ron

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center

Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu
----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 12/07/2007 03:45 PM -----

Sharon Gonzales/Pediatrics/mc/Duke

12/07/2007 03:43 PM

To

Ronald N Goldberg/Pediatrics/mc/Duke

cc

Subject

Proposal

Sharon H. Gonzales
Department of Pediatrics
Division of Neonatology
DUMC Box 3179
Durham, NC 27710
Phone: 919-668-1592
Fax: 919-681-6065
gonza025@mc.duke.edu

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Thursday, January 10, 2008 1:23:00 PM

But the info is available (b) (5) [redacted] there and not a problem for the trial

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Sent: Thu Jan 10 13:21:21 2008
Subject: Re: SUPPORT

Folks are quite concerned about (b) (5) [redacted]

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Jan 10 13:15:43 2008
Subject: Re: SUPPORT

Interesting-my understanding is that the irbs expect any new available information that is pertinent for an ongoing study to be reported to them. Sitting on the nichd irb, this is part of our annual review and an ongoing thing we review...

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Sent: Thu Jan 10 13:08:07 2008
Subject: SUPPORT

Cathy
The steering committeee discussed the HOT TOPICs presentation - the slides now on the web are slightly different than the handout. (b) (5) [redacted] I will get back to you on this. Dr. Blaisdell from nhlbi was here and part of the discussion and was in agreement.
More to follow
Rose

Sent from my BlackBerry Wireless Handheld

From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Wednesday, January 09, 2008 9:24:59 PM

---

yes-pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/8/08 8:41:01 AM >>>
Hi,

I have two requests for investigators to use the pulmonary outcomes questionnaire for studies in development. Robert Ballard requests to use this instrument in her TOLSURF Trial and Rich Parad and Jon Davis request to use this in their recombinant SOD trial. I have attached summaries from both studies. The Investigators from the Tucson Asthma study had given us permission to use and modify their questionnaire and have also granted permission for further use by these two investigative teams. Please send me a yes/no vote by January 18.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

6100 Executive Blvd., Room 4B03B

MSC 7510

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Finer, Neil
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Finer, Neil; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; Rich, Wade
Subject:	FW: SUPPORT materials Steering Comm Jan 10 08
Date:	Wednesday, January 09, 2008 7:00:15 PM
Attachments:	All Centers pct in range through Dec07.rtf January2008UpdateHINTZ.DOC

Hi Everyone
I thought that I sent these out yesterday but I can't find the email
Two more attachments for the meeting
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

From: Neil Finer
Sent: Thursday, October 11, 2007 9:11 AM
To: Neil Finer; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'
Subject: FW: SUPPORT materials
Hi Everyone
Here is an agenda for next weeks meeting, and the updates from Marie (Thanks Marie)

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations (Currently 815 per August > 60% of total, slightly >2/center/mo for 2007)

1. Discuss Eye follow-up and the 55 day rule

4. Review status of Secondaries-
   MRI
   Breathing Outcomes
   Nutrition
   Antenatal consent

5. Discuss Prospective Meta Analysis
6. Other Issues

Please let me know if there are additional issues you would like added to the agenda
Neil

Neil N. Finer, M.D.
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PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 01/07/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Oct07-Dec07	Days of life 1-14	All centers	8163	31.5	8.7	77.5	13.8
		Center 3	900	37.0	7.3	78.8	13.9
		Center 5	2106	28.5	8.4	69.6	22.0
		Center 15	502	25.7	14.6	75.2	10.2
		Center 16	2181	40.2	9.3	84.7	6.0
	Day 15 to 36 wks	All centers	32506	24.8	12.5	65.8	21.7
		Center 3	1684	19.6	16.5	59.0	24.5
		Center 5	7525	23.1	11.0	62.0	27.0
		Center 11	1124	24.5	10.2	54.1	35.7
		Center 14	1261	20.1	13.8	64.3	21.8
		Center 15	3128	22.9	18.6	64.4	17.0
		Center 16	5863	27.9	13.6	70.7	15.7
		Center 23	2380	27.4	11.2	60.0	28.8
		Center 25	5842	25.2	9.6	73.0	17.4
Jul07-Sep07	Days of life 1-14	All centers	14378	33.7	7.5	75.7	16.8
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1394	34.8	9.6	74.8	15.6
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9
		Center 16	1162	39.8	7.4	81.8	10.7
		Center 23	2150	32.6	5.5	71.6	23.0
		Center 25	1723	39.7	5.9	83.1	11.0
	Day 15 to 36 wks	All centers	53666	24.9	11.6	65.3	23.2
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 01/07/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5289	22.4	10.0	60.0	30.0
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	14959	34.4	9.0	76.7	14.2
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1061	31.1	11.6	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1428	40.5	8.0	86.1	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	685	16.3	7.9	69.3	22.8
	Day 15 to 36 wks	All centers	52886	28.7	12.1	66.0	21.9
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		Center 11	4086	23.7	10.1	57.7	32.2
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	3165	26.9	12.7	71.1	16.2
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 01/07/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent in [illegible]
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2014	27.8	7.7	57.4	34.9
Jan07-Mar07	Days of life 1-14	All centers	16747	35.4	8.4	78.1	13.5
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	53147	28.0	12.3	68.9	18.8
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8
		Center 16	3353	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	3246	21.2	17.4	62.5	20.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 01/07/08)

Months	Time on supplemental oxygen	Site	Number of 2+ hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Mar06-Dec06	Days of life 1-14	All centers	32501	37.4	8.2	79.0	12.9
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2419	33.1	9.1	67.5	23.4
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5667	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	853	30.9	6.2	79.1	14.8
		Center 25	1138	48.0	6.4	83.5	10.1
	Day 15 to 36 wks	All centers	106405	29.2	12.6	68.4	19.0
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3287	29.6	11.7	72.8	15.5
		Center 11	5915	29.9	10.4	61.4	28.2
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14380	29.2	12.5	69.1	18.5
		Center 18	15398	23.7	17.0	66.0	17.0
		Center 19	881	20.1	9.1	55.9	35.0
		Center 25	6484	39.9	9.3	77.0	13.7
Through Feb06	Days of life 1-14	All centers	26933	37.8	9.4	79.4	11.2
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 01/07/08)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1509	31.2	10.2	77.0	12.9
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1229	38.1	10.6	84.8	4.6
		Center 22	3531	40.0	8.7	79.9	11.3
	Day 15 to 36 wks	All centers	136883	26.5	12.3	67.8	20.0
		Center 3	15229	19.9	17.1	64.8	18.1
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	4802	17.3	8.5	58.1	33.4
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	11637	26.4	17.3	66.4	16.4
		Center 19	1919	32.8	7.0	73.3	19.8
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	2450	27.4	17.8	70.3	11.9
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

1) Enrollment/MRI central reading update

- From monthly report and additional routine data query from RTI (through 11/31/2007)
  - **337 patients** have been enrolled
    - 35-42 week neuroimaging *including MRI* is complete for ~**242 patients**
      - **Of the 95 patients enrolled without MRI:**
        - 48 patients died before MRI
        - 31 with MRI01 not yet complete or window not reached
        - 16 with other issues
- MRI central reading is ongoing –
  - Approximately 165 MRIs have been read or are in process with the central reader (Dr. Barnes); additional 50 MRI's sent by RTI this week
  - THANK YOU to all sites for their diligence in sending MRI's and CUS on a routine basis to RTI

2) New site to SUPPORT Neuroimaging Secondary roster

- EMORY received IRB approval on 11/20/07

3) Tracking enrollment

- THANK YOU to all the coordinators who are keying the FIRST PART of the MRI01 form as soon as they can.

4) Please call or email with questions, comments, and suggestions

Susan Hintz
650-723-5711 (office)
Email: srhintz@stanford.edu

THANKS TO ALL THE SITES FOR THEIR HARD WORK ON THIS STUDY!

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 11:44:08 PM

Yes
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 6:41 AM
To: Finer, Neil; Rich, Wade; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Stevens, Timothy; Phelps, Dale
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Please send me a yes/no vote by January 18.

Thanks
Rose

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higginsr@mail.nih.gov

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 2:40:39 PM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 1/8/2008 9:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Stevens, Timothy; Phelps, Dale
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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: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 1:32:22 PM

---

yes

Ronald N. Goldberg, M.D.
Shaad-McBryde Professor of Pediatrics
Chief, Neonatal-Perinatal Medicine
Box 3179
Duke University Medical Center
Durham, NC 27710
Phone: 919-681-6037
Fax: 919-681-6065
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

01/08/2008 09:41 AM

To <nfiner@ucsd.edu>, <wrich@ucsd.edu>, "nancy newman" <nxs5@case.edu>, "Gantz, Marie" <mgantz@rti.org>, <rohls@unm.edu>, <alaptook@WIHRI.org>, "Abhik Das" <adas@rti.org>, <ambal@uab.edu>, <aaf2@po.cwru.edu>, <Bradley.yoder@hsc.utah.edu>, "Brenda Poindexter" <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, "Ed Bell" <Edward-bell@uiowa.edu>, "Ed Donovan" <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Ivan Frantz" <IFrantz@Tufts-NEMC.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Krisa VanMeurs (VanMeurs, Krisa)" <vanmeurs@leland.stanford.edu>, "Kristi Watterberg" <kwatterberg@salud.unm.edu>, <kurt.schibler@cchmc.org>, <cotte010@mc.duke.edu>, "Michelle Walsh" <mcw3@po.cwru.edu>, "Mickey Caplan" <mca113@Northwestern.edu>, "Oh William (E-mail)" <william_oh@brown.edu>, "Pablo Sanchez" <Pablo.Sanchez@UTSouthwestern.edu>, "Poole Kenneth (E-mail)" <poo@rti.org>, "Roger Faix" <Roger.Faix@hsc.utah.edu>, "Ronald GOldberg" <goldb008@mc.duke.edu>, "Seetha Shankaran" <sshankar@med.wayne.edu>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)" <barbara_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>

cc "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>, "Newman, Jamie" <newman@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Huitema, Carolyn Petrie" <petrie@rti.org>, "Stevens, Timothy" <Timothy_Stevens@URMC.Rochester.edu>, "Phelps, Dale" <Dale_Phelps@URMC.Rochester.edu>

Subject Requests to use SUPPORT Pulmonary outcomes questionnaire

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higginsr@mail.nih.gov

[attachment "Ballard request.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]
[attachment "Parad.Davis request.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 10:42:32 AM

Yes

Jon E. Tyson, MD, MPH
Center for Clinical Research & Evidence-Based Medicine
UT Medical School at Houston
6431 Fannin St., MSB 2.106
Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 8:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E
Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Stevens, Timothy; Phelps, Dale
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higginsr@mail.nih.gov

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 11:41:15 AM

Rose
My vote is yes
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 9:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
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Thanks
Rose

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higginsr@mail.nih.gov

From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 10:36:38 AM

Yes.

Krisa

>Hi,
>I have two requests for investigators to use the
>pulmonary outcomes questionnaire for studies in
>development. Robert Ballard requests to use
>this instrument in her TOLSURF Trial and Rich
>Parad and Jon Davis request to use this in their
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>Thanks
>Rose
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>301-435-7909
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><mailto:higginsr@mail.nih.gov>higginsr@mail.nih.gov
>
>
>Content-Type: application/msword;
> name="Ballard request.doc"
>Content-Description: Ballard request.doc
>Content-Disposition: attachment;
> filename="Ballard request.doc"
>
>Attachment converted: KVM PowerBook :Ballard
>request.doc (WDBN/«IC») (000FCFD8)
>Content-Type: application/msword;
> name="Parad.Davis request.doc"
>Content-Description: Parad.Davis request.doc
>Content-Disposition: attachment;
> filename="Parad.Davis request.doc"
>

>Attachment converted: KVM PowerBook :Parad.Davis
>request.doc (WDBN/«IC») (000FCFD9)

From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 10:12:41 AM

Hi Rose,
I vote yes to share pulmonary outcomes questionnaire with these investigators.
Thanks and see you Thursday!
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229
USA
TEL: 513-872-3007
PAGER: 513-736-5649
E-mail: kurt.schibler@cchmc.org

On 1/8/08 9:41 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
> I have two requests for investigators to use the pulmonary outcomes questionnaire for studies in development. Robert Ballard requests to use this instrument in her TOLSURF Trial and Rich Parad and Jon Davis request to use this in their recombinant SOD trial. I have attached summaries from both studies. The Investigators from the Tucson Asthma study had given us permission to use and modify their questionnaire and have also granted permission for further use by these two investigative teams. **Please send me a yes/no vote by January 18.**
>
> Thanks
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> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 9:52:51 AM

Rose:
YES!

I think you should keep track of this request as it is a huge service to the neonatology community worldwide. I think we should also make it clear to everyone in the field that this sort of request is welcome.

Maybe something to discuss at some point in the SC meeting briefly to get the ideas from the group.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 8:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Wally Carlo, M.D.; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail)
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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Requests to use SUPPORT Pulmonary outcomes questionnaire
Date: Tuesday, January 08, 2008 9:49:40 AM

Yes

Kathleen A. Kennedy, MD, MPH
Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
(713) 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 08, 2008 8:41 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; nancy newman; Gantz, Marie; rohls@unm.edu; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E
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Thanks
Rose

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From:	Finer, Neil
To:	Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Finer, Neil; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject:	SUPPORT Meeting Agenda Jan 10 08
Date:	Monday, January 07, 2008 5:26:56 PM
Attachments:	SUPPORT Enrollment 12-27-2007.doc Tables Prepared for Dec07 DSMC Meeting.doc SUPPORT Adverse Events 12-27-07.doc SUPPORT Protocol Deviations by center - old vs new 12-27-07.doc SUPPORT Protocol Deviations - old vs new 12-27-07.doc All Centers pct in range through Dec07.rtf

Hi Everyone
Here is an agenda for next weeks meeting, and the updates from Marie (Thanks Marie)

Agenda - Support Subcommittee Meeting / Steering Committee Meeting

1. Review Enrollments to date, adverse events, and protocol deviations (Currently 884 per August 67% of total)
2. Review the Physiologic Oxygen Challenge requirements for infants at altitude as a result of last weeks teleconference.
3. Review for information the information provided to the DSMC - Attached
4. Review status of Secondaries-
   MRI
   Breathing Outcomes
   Nutrition
   Antenatal consent
5. Other Issues

Please let me know if there are additional issues you would like added to the agenda

Neil N. Finer, M.D.
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Director, Division of Neonatal-Perinatal Medicine
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543-3759
Facsimile: 619.543.3812

SUPPORT Enrollment as of December 27, 2007

Total Enrolled

	N	% of total (1310)
Enrolled	884	67%

Enrollment by Center

Center	<Jul-07	Jul-07	Aug-07	Sep-07	Oct-07	Nov-07	Dec-07	Total
3	65	4	1	1	4	3	1	79
4	42	1	0	1	1	1	0	46
5	22	4	1	3	3	3	2	38
8	17	0	0	0	0	0	0	17
9	50	3	4	0	2	0	0	59
11	51	1	8	2	1	2	0	65
12	40	2	5	1	1	2	0	51
13	19	0	1	0	0	1	0	21
14	68	0	6	4	0	1	3	82
15	24	0	1	5	0	3	1	34
16	101	2	0	5	4	6	3	121
18	51	2	1	4	0	2	1	61
19	36	2	1	2	2	1	0	44
20	9	0	0	0	0	0	0	9
21	8	0	0	0	0	0	0	8
22	50	2	0	0	1	1	0	54
23	28	5	2	2	1	1	1	40
24	11	0	0	0	1	4	0	16
25	15	2	5	4	1	2	0	29
26	6	1	1	0	2	0	0	10
Total	713	31	37	34	24	33	12	884
Centers		17	17	17	17	17	17	
Avg/center		1.8	2.2	2.0	1.4	1.9	0.7	

Months Needed to Complete Enrollment

Average enrolled per center per month	Number of months needed
2	13
2.5	10
3	8

Tables Prepared for December 2007 DSMC Meeting

Category		Number	Percent
Screened		2169	100%
Eligible		1925	89%
Consented		897	41%
Randomized	% of Screened	851	39%
	% of Eligible		44%
	% of Consented		95%
Eligible – Not randomized			
Infants		1074	100%
Reason – Parent unavailable		155	14.4%
Reason – Parent refusal		449	41.8%
Reason – Consent not requested		415	38.6%
Reason – Physician refusal		8	0.7%
Reason – Too old at delivery		8	0.7%
Reason – Parent withdrew consent		4	0.4%
Reason – Precipitous delivery		4	0.4%
Reason – Emerging medical issues		5	0.5%
Reason – Other		26	2.4%

SUPPORT Enrollment as of November 21, 2007

Category	Center										Total
Infants screened	146	110	125	33	152	247	175	105	179	69	2169
% Eligible	96%	72%	98%	97%	93%	94%	79%	89%	79%	99%	89%
% Consented	57%	43%	29%	58%	40%	27%	28%	20%	45%	52%	41%
Randomized											
Number of infants	76	45	35	17	59	63	48	20	79	32	851
% of Screened	52%	41%	28%	52%	39%	26%	27%	19%	44%	46%	39%
% of Eligible	54%	57%	28%	53%	42%	27%	35%	22%	56%	47%	44%
% of Consented	92%	96%	97%	89%	97%	94%	98%	95%	98%	89%	95%
Eligible, not randomized											
Number of infants	64	34	88	15	82	169	91	73	62	36	1074
% Parent unavailable	5%	0%	5%	13%	12%	36%	9%	42%	3%	33%	14%
% Parent refusal	27%	32%	42%	60%	45%	47%	33%	23%	37%	42%	42%
% Consent not requested	55%	59%	52%	13%	40%	14%	56%	33%	52%	14%	39%
% Physician refusal	3%	0%	0%	0%	0%	1%	1%	0%	5%	0%	1%
% Too old at delivery	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%	1%
% Parent w/drew consent	2%	0%	0%	0%	0%	0%	0%	0%	0%	6%	0%
% Precipitous delivery	0%	0%	0%	0%	1%	0%	0%	0%	0%	3%	0%
% Medical issues	3%	3%	0%	0%	0%	0%	0%	0%	0%	0%	0%
% Other reason	6%	6%	0%	13%	1%	2%	1%	1%	3%	3%	2%

Category	Center										Total
Infants screened	169	147	113	20	29	104	59	53	102	32	2169
% Eligible	95%	96%	92%	100%	28%	82%	100%	89%	83%	88%	89%
% Consented	73%	44%	41%	45%	28%	50%	68%	28%	28%	31%	41%
Randomized											
Number of infants	117	58	43	9	8	52	39	14	27	10	851
% of Screened	69%	39%	38%	45%	28%	50%	66%	26%	26%	31%	39%
% of Eligible	73%	41%	41%	45%	100%	61%	66%	30%	32%	36%	44%
% of Consented	94%	91%	93%	100%	100%	100%	98%	93%	93%	100%	95%
Eligible, not randomized											
Number of infants	43	83	61	11	0	33	20	33	58	18	1074
% Parent unavailable	7%	1%	2%	9%	---	36%	0%	0%	7%	6%	14%
% Parent refusal	63%	33%	70%	45%	---	36%	65%	42%	40%	50%	42%
% Consent not requested	14%	59%	21%	45%	---	27%	30%	55%	50%	44%	39%
% Physician refusal	0%	0%	2%	0%	---	0%	0%	0%	0%	0%	1%
% Too old at delivery	16%	0%	0%	0%	---	0%	0%	0%	0%	0%	1%
% Parent w/drew consent	0%	1%	0%	0%	---	0%	0%	0%	0%	0%	0%
% Precipitous delivery	0%	0%	2%	0%	---	0%	5%	0%	0%	0%	0%
% Medical issues	0%	1%	0%	0%	---	0%	0%	3%	0%	0%	0%
% Other reason	0%	5%	3%	0%	---	0%	0%	0%	3%	0%	2%

Infants Screened, Eligible, Consented and Randomized, by Center

Characteristic	Randomized (N=851)	Not randomized (N=1040†)	P-value
Infant Characteristics			
GA: 24-25 weeks	42% (356/843)	47% (488/1040)	0.0417*
Birth Weight (grams)	827.1 ± 198.7	808.0 ± 186.5	0.0320*
Small for gestational age	8% (69/843)	8% (88/1040)	0.8291
Gender: Male	53% (449/843)	51% (535/1040)	0.4318
Maternal/Delivery Characteristics			
Ethnicity: Hispanic	19% (157/820)	17% (168/1011)	0.1590
Race: White	57% (476/838)	52% (531/1019)	0.0434*
Race: Black	39% (329/838)	43% (441/1019)	0.0803
Multiple birth	26% (223/843)	23% (243/1039)	0.1255
C-section	65% (548/842)	69% (713/1040)	0.1109
Maternal age	27.1 ± 6.5	27.3 ± 6.7	0.5699
Parity	2.3 ± 1.5	2.2 ± 1.6	0.2911
Insurance: Medicaid	53% (435/826)	47% (480/1016)	0.0207*
Preeclampsia/eclampsia/ hypertension	26% (215/843)	22% (226/1040)	0.0545
Antenatal steroids	96% (807/842)	86% (890/1034)	<0.0001*

Characteristics of Eligible Infants Randomized vs. Not Randomized

† An additional 24 infants were excluded because they were not born in the 24-27 week GA window, and 10 were excluded because no GDB data were available.

Percent of SUPPORT infants with selected adverse events as of December 27, 2007*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	5.9	8.8	3.8
Air leak	8.3	11.2	6.3
Pulmonary hemorrhage	6.2	9.3	4.1
Severe IVH (grades III-IV)	13.8	19.0	10.3

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers* (Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information (SUPP03/NG02), denominator for air leak and pulmonary hemorrhage is number of infants with NICU data (NG03), denominator for severe IVH is number of infants with head ultrasound (SUPP09/NG03).

SUPPORT Trial Protocol Deviations, by Center, for Infants Born January 1, 2006 – December 27, 2007

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			1									1									2
Surfactant not given in the first hour	2	2				4	1	2	2		5		1					4	4		27
Oximeter not started within 2 hours	1	1				1	2			2	1	1	1			1	2	1	2	1	17
Infant placed on study oximeter for incorrect treatment	1		1			1					2		1				1		1		8
Failure to use study oximeter at times required by protocol	2	4	6		2	3	5	1	6		5		2				3	3	8	3	53
Non-study (unmasked) oximeter used at same time as study ox.						2	1			1									1		5
Mechanical ventilation initiated for other than study criteria																	2				2
NSIMV initiated in infant not previously intubated	1				1						4										6
Extubation (excluding unplanned) for other than study criteria						3			4												7
Failure to extubate CPAP infant if all criteria met								1		2											3
Failure to extubate surfactant infant if all criteria met						1															1
High flow nasal cannula used on CPAP infant within first 14 days	3	10	4		20	7	9	3	11	1	4	10	8			1	1	1	6		99
Infant received postnatal steroids in first 21 days of life						2		1	4		2	7	1				1				18
Randomization/consent errors	1	1	1		3	1				1		3				1	4				16
Other									1	1											3
Total	11	18	13	0	26	25	18	8	28	8	23	22	14	0	0	3	14	9	23	4	267

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born January 1, 2006 – December 27, 2007

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol			3%									2%									0%
Surfactant not given in the first hour	4%	6%				9%	2%	10%	3%		6%		3%					25%	14%		4%
Oximeter not started within 2 hours	2%	3%				2%	5%			6%	1%	2%	3%			8%	5%	6%	7%	10%	3%
Infant placed on study oximeter for incorrect treatment	2%		3%			2%					2%		3%				3%		3%		2%
Failure to use study oximeter at times required by protocol	4%	11%	16%		4%	7%	12%	5%	10%		6%		7%				8%	19%	28%	30%	8%
Non-study (unmasked) oximeter used at same time as study ox.						4%	2%			3%									3%		1%
Mechanical ventilation initiated for other than study criteria																	5%				0%
NSIMV initiated in infant not previously intubated	2%				2%						5%										1%
Extubation (excluding unplanned) for other than study criteria						7%			7%												1%
Failure to extubate CPAP infant if all criteria met								5%		6%											1%
Failure to extubate surfactant infant if all criteria met						2%															0%
High flow nasal cannula used on CPAP infant within first 14 days	5%	28%	11%		43%	15%	22%	15%	18%	3%	5%	24%	28%			8%	3%	6%	21%		12%
Infant received postnatal steroids in first 21 days of life						4%		5%	7%		2%	17%	3%				3%				3%
Randomization/consent errors	2%	3%	3%		7%	2%				3%		7%				8%	10%				2%
Other									2%	2%									2%		1%
Total protocol deviations	20%	50%	34%		57%	54%	44%	40%	47%	25%	28%	52%	48%		0%	23%	35%	56%	79%	40%	42%
Total number of infants enrolled	55	36	38	0	46	46	41	20	60	32	83	42	29	0	1	13	40	16	29	10	637

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											1										1
Surfactant not given in the first hour	4			1		2	1				1										9
Oximeter not started within 2 hours						1					5	1									7
Infant placed on study oximeter for incorrect treatment	1			1							4					1					7
Failure to use study oximeter at times required by protocol	2	1				2			4		2	1		1	1						14
Non-study (unmasked) oximeter used at same time as study ox.															1						1
Mechanical ventilation initiated for other than study criteria																					0
NSIMV initiated in infant not previously intubated		1									1										2
Extubation (excluding unplanned) for other than study criteria											1				1						2
Failure to extubate CPAP infant if all criteria met		1														2					3
Failure to extubate surfactant infant if all criteria met						1															1
High flow nasal cannula used on CPAP infant within first 14 days						1			1			1									3
Infant received postnatal steroids in first 21 days of life											1					4					5
Randomization/consent errors		1											1	2							4
Other																					2
Total	7	4	0	2	0	8	1	0	5	0	17	3	1	3	3	7	0	0	0	0	61

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations as a Percent of Infants Enrolled, by Center, for Infants Born Through December 31, 2005

Type of protocol deviation	Center																				Total
	3	4	5	8	9	11	12	13	14	15	16	18	19	20	21	22	23	24	25	26	
CPAP not initiated if required by protocol											3%										0%
Surfactant not given in the first hour	17%			6%		11%	10%				3%										4%
Oximeter not started within 2 hours						5%					13%	5%									3%
Infant placed on study oximeter for incorrect treatment	4%			6%							11%					2%					2%
Failure to use study oximeter at times required by protocol	8%	10%				11%			18%		5%	5%		11%	14%						8%
Non-study (unmasked) oximeter used at same time as study ox.															14%						1%
Mechanical ventilation initiated for other than study criteria																					0%
NSIMV initiated in infant not previously intubated		10%									3%										1%
Extubation (excluding unplanned) for other than study criteria											3%				14%						1%
Failure to extubate CPAP infant if all criteria met		10%														5%					1%
Failure to extubate surfactant infant if all criteria met						5%															0%
High flow nasal cannula used on CPAP infant within first 14 days						5%			5%			5%									12%
Infant received postnatal steroids in first 21 days of life											3%					10%					3%
Randomization/consent errors		10%											7%	22%							2%
Other						5%					3%										1%
Total protocol deviations	29%	40%		12%	0%	42%	10%	0%	23%	0%	45%	16%	7%	33%	43%	17%					37%
Total number of infants enrolled	24	10	0	17	13	19	10	1	22	2	38	19	15	9	7	41	0	0	0	0	247

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations for Infants Born January 1, 2006 – December 27, 2007

Type of protocol deviation	Number
CPAP not initiated if required by protocol	2
Surfactant not given in the first hour	27
Oximeter not started within 2 hours	17
Infant placed on study oximeter for incorrect treatment	8
Failure to use study oximeter at times required by protocol	53
Non-study (unmasked) oximeter used at same time as study oximeter	5
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	7
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
High flow nasal cannula used on CPAP infant within first 14 days of life	99
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	16
Other	3
Total	267

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	46
Infant placed on study oximeter for incorrect treatment	8
Failure to use study oximeter at times required by protocol	53
Non-study (unmasked) oximeter used at same time as study oximeter	5
Mechanical ventilation initiated for other than study criteria	2
NSIMV initiated in infant not previously intubated	6
Extubation (excluding unplanned) for other than study criteria	7
Failure to extubate infant if all criteria met	4
High flow nasal cannula used on CPAP infant within first 14 days of life	99
Infant received postnatal steroids in first 21 days of life	18
Randomization/consent errors	16
Other	3
Total	267

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

SUPPORT Trial Protocol Deviations for Infants Born Through December 31, 2005

Type of protocol deviation	Number
CPAP not initiated if required by protocol	1
Surfactant not given in the first hour	9
Oximeter not started within 2 hours	7
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
High flow nasal cannula used on CPAP infant within first 14 days of life	3
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	61

Type of protocol deviation (some categories collapsed)	Number
Assigned arm not implemented within required amount of time	17
Infant placed on study oximeter for incorrect treatment	7
Failure to use study oximeter at times required by protocol	14
Non-study (unmasked) oximeter used at same time as study oximeter	1
Mechanical ventilation initiated for other than study criteria	0
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	2
Failure to extubate infant if all criteria met	4
High flow nasal cannula used on CPAP infant within first 14 days of life	3
Infant received postnatal steroids in first 21 days of life	5
Randomization/consent errors	4
Other	2
Total	61

Includes protocol deviations reported on SUPP06 as well as deviations gathered from other forms.

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/14/07)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Oct07-Dec07	Days of life 1-14	All centers	6360	31.3	8.8	77.2	14.0
		Center 3	900	37.0	7.3	78.8	13.9
		Center 5	1477	28.6	8.0	69.9	22.2
		Center 15	500	25.8	14.7	75.5	9.8
		Center 16	1647	44.4	8.7	84.5	6.8
	Day 15 to 36 wks	All centers	26397	25.7	12.2	66.5	21.3
		Center 3	1684	19.6	16.5	59.0	24.5
		Center 5	4535	26.0	10.5	65.5	24.0
		Center 11	1124	24.5	10.2	54.1	35.7
		Center 14	1255	20.2	13.8	64.3	21.9
		Center 15	2303	26.4	17.3	65.3	17.4
		Center 16	4034	26.4	13.9	70.1	16.0
		Center 23	2380	27.4	11.2	60.0	28.8
		Center 25	5691	25.6	7	73.2	17.5
Jul07-Sep07	Days of life 1-14	All centers	14378	33.7	7.5	75.7	16.8
		Center 3	916	35.8	6.9	67.1	26.0
		Center 5	1676	20.7	5.3	61.1	33.6
		Center 11	1394	34.8	9.6	74.8	15.6
		Center 12	1199	27.6	8.6	78.8	12.6
		Center 14	746	44.5	5.3	84.9	9.8
		Center 15	539	38.2	15.1	78.0	6.9
		Center 16	1162	39.8	7.4	81.8	10.7
		Center 23	2150	32.6	5.5	71.6	23.0
		Center 25	1723	39.7	5.9	83.1	11.0
	Day 15 to 36 wks	All centers	53666	24.9	11.6	65.3	23.2
		Center 3	6172	24.8	17.2	61.0	21.8
		Center 5	6962	24.0	7.9	64.9	27.3
		Center 9 site A	2329	22.3	13.6	63.1	23.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/14/07)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site B	3515	29.5	13.5	71.5	14.9
		Center 11	5289	22.4	10.0	60.0	30.0
		Center 12	5098	22.2	9.7	64.9	25.4
		Center 14	861	36.8	7.3	71.1	21.6
		Center 16	1170	20.3	14.5	67.6	17.9
		Center 23	7333	22.5	10.8	57.5	31.7
		Center 25	6691	27.5	11.0	71.4	17.5
Apr07-Jun07	Days of life 1-14	All centers	14959	34.4	9.0	76.7	14.2
		Center 3	1553	27.3	14.5	74.4	11.1
		Center 4	822	45.7	7.0	84.2	8.9
		Center 5	1253	31.3	9.1	69.6	21.3
		Center 9 site A	1061	31.1	11.6	74.2	14.3
		Center 9 site B	1048	53.7	5.8	87.1	7.1
		Center 11	1493	29.0	10.3	69.5	20.1
		Center 12	1773	30.4	9.1	73.6	17.3
		Center 14	1382	41.5	7.0	80.3	12.8
		Center 16	1428	40.5	8.0	86.1	5.8
		Center 23	701	25.9	5.2	76.1	18.8
		Center 26	685	16.3	7.9	69.3	22.8
	Day 15 to 36 wks	All centers	52886	28.7	12.1	66.0	21.9
		Center 3	4261	23.1	21.6	61.5	16.9
		Center 4	2571	23.9	13.0	71.1	15.9
		Center 5	5156	28.1	14.7	64.9	20.4
		Center 9 site A	2392	21.3	14.4	64.9	20.8
		Center 9 site B	3605	43.6	12.1	77.4	10.5
		Center 11	4086	23.7	10.1	57.7	32.2
		Center 12	6509	25.2	9.5	55.9	34.6
		Center 13	3165	26.9	12.7	71.1	16.2
		Center 14	8919	30.7	12.6	71.5	16.0
		Center 15	574	34.8	9.1	70.2	20.7
		Center 16	1538	47.4	5.7	84.9	9.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/14/07)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 23	2897	21.1	6.2	58.9	35.0
		Center 26	2014	27.8	7.7	57.4	34.9
Jan07-Mar07	Days of life 1-14	All centers	16747	35.4	8.4	78.1	13.5
		Center 3	1035	31.2	11.0	73.6	15.4
		Center 4	1363	34.8	7.2	82.1	10.6
		Center 5	824	33.6	11.3	68.9	19.7
		Center 11	1300	27.6	9.0	74.5	16.5
		Center 12	996	35.1	5.4	79.4	15.2
		Center 13	1265	34.9	4.7	81.3	14.0
		Center 14	2049	36.4	7.7	84.2	8.1
		Center 15	1259	33.7	7.2	78.6	14.2
		Center 16	2259	45.2	9.8	81.0	9.2
		Center 22	746	35.4	8.0	74.3	17.6
		Center 23	906	35.3	6.1	72.8	21.1
		Center 24	1008	45.0	6.8	75.8	17.4
	Day 15 to 36 wks	All centers	53147	28.0	12.3	68.9	18.8
		Center 3	4656	27.1	18.0	62.3	19.6
		Center 4	3884	30.6	9.5	73.9	16.6
		Center 5	2472	29.8	16.6	62.5	21.0
		Center 9 site A	2188	20.0	14.6	60.9	24.5
		Center 11	2232	28.0	10.4	71.9	17.7
		Center 12	7802	21.2	13.5	69.0	17.5
		Center 13	4975	26.0	7.2	72.2	20.6
		Center 14	5426	31.2	12.8	75.8	11.4
		Center 15	3579	33.8	8.5	68.7	22.8
		Center 16	3353	30.8	14.5	69.2	16.3
		Center 22	689	31.4	7.8	68.3	23.9
		Center 23	2027	20.1	9.4	65.9	24.7
		Center 24	3246	21.2	17.4	62.5	20.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL O2 ONLY

(OXIMETER DATA PROCESSED AS OF 12/14/07)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	[illegible]
Mar06-Dec06	Days of life 1-14	All centers	32501	37.4	8.2	79.0	12.9
		Center 3	4105	43.6	7.7	80.1	12.1
		Center 4	1852	41.0	6.8	84.8	8.4
		Center 5	1113	37.0	10.3	80.0	9.7
		Center 9 site A	1736	34.7	9.6	72.9	17.5
		Center 9 site B	761	43.4	8.4	82.4	9.2
		Center 11	2419	33.1	9.1	67.5	23.4
		Center 12	2877	31.3	6.8	78.3	14.9
		Center 14	3367	38.5	8.3	81.7	10.0
		Center 15	819	43.3	4.7	77.4	17.9
		Center 16	5667	41.4	8.0	84.8	7.3
		Center 18	4448	31.6	9.0	75.0	15.9
		Center 19	853	30.9	6.2	79.1	14.8
		Center 25	1138	48.0	6.4	83.5	10.1
	Day 15 to 36 wks	All centers	106405	29.2	12.6	68.4	19.0
		Center 3	14994	33.4	15.1	69.0	15.9
		Center 4	7238	30.4	11.5	70.9	17.6
		Center 5	4399	23.5	17.8	65.9	16.3
		Center 9 site A	5818	30.6	13.4	68.7	17.9
		Center 9 site B	3287	29.6	11.7	72.8	15.5
		Center 11	5915	29.9	10.4	61.4	28.2
		Center 12	10913	24.9	9.3	65.3	25.3
		Center 14	11596	30.1	11.1	71.5	17.4
		Center 15	2791	36.0	8.3	71.2	20.6
		Center 16	14380	29.2	12.5	69.1	18.5
		Center 18	15398	23.7	17.0	66.0	17.0
		Center 19	881	20.1	9.1	55.9	35.0
		Center 25	6484	39.9	9.3	77.0	13.7
Through Feb06	Days of life 1-14	All centers	26933	37.8	9.4	79.4	11.2
		Center 3	1886	28.9	14.9	77.2	7.9
		Center 8	1448	29.6	6.6	73.3	20.1

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH DECEMBER 2007

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 12/14/07)

Months	Time on supplemental oxygen	Site	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
		Center 9 site A	1920	36.1	12.2	76.9	11.0
		Center 11	1947	36.9	9.3	75.6	15.1
		Center 12	1848	46.7	6.2	82.5	11.3
		Center 14	3171	38.4	8.8	83.1	8.1
		Center 16	5580	42.6	9.4	81.4	9.2
		Center 18	1509	31.2	10.2	77.0	12.9
		Center 20	1860	30.8	7.5	74.1	18.4
		Center 21	1229	38.1	10.6	84.8	4.6
		Center 22	3531	40.0	8.7	79.9	11.3
	Day 15 to 36 wks	All centers	136883	26.5	12.3	67.8	20.0
		Center 3	15229	19.9	17.1	64.8	18.1
		Center 4	5686	20.6	7.4	64.9	27.7
		Center 8	4802	17.3	8.5	58.1	33.4
		Center 9 site A	10780	26.7	13.5	66.6	19.8
		Center 11	10209	27.5	10.3	67.1	22.7
		Center 12	9532	33.3	10.0	72.9	17.0
		Center 14	19113	25.5	11.8	70.3	17.9
		Center 16	16900	30.8	12.3	71.7	16.0
		Center 18	11637	26.4	17.3	66.4	16.4
		Center 19	1919	32.8	7.0	73.3	19.8
		Center 20	9055	20.5	11.6	63.2	25.2
		Center 21	2450	27.4	17.8	70.3	11.9
		Center 22	17931	29.8	10.1	67.5	22.4

Center shown only if the center had 5+ infants (at least 1 in each oximeter group) and 500+ hours in the time period

From: Tyson, Jon E
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Publications | Tyson abstracts
Date: Monday, January 07, 2008 10:39:26 AM

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1. Published : Kennedy KA, Stoll BJ, Ehrenkranz RA, Oh W, Wright LL, Stevenson DK, Lemons JA, Sowell A, Mele L, Tyson JE, and Verter J. Vitamin A to prevent bronchopulmonary dysplasia in very-low-birth weight infants: has the dose been too low? The NICHD Neonatal Research Network. Early Hum Dev 49:19-31, 1997.
2. No manuscript published, partly because of me, partly because of fault of the biostatistics center at that time, and partly because this is a difficult albeit methodological issue with no obvious journal that would be interested.
3) The issue in this abstract was addressed in:

   Tyson JE, Younes N, Verter J, and Wright LL. Viability, morbidity, and resource use among newborns of 501-800 g birth weight. National Institute of Child Health and Human Development Neonatal Research Network. JAMA 276:1645-1651, 1996.

4) The issue in this abstract was included in issues addressed in: Tyson JE, Parikh NA, Langer J, Green C, Higgins R: Intensive Care for Extremely Premature Newborns:Moving Beyond Gestational Age Thresholds. N Engl J Med in press.

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From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, January 07, 2008 8:12 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Tyson, Jon E
Cc: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Publications | Tyson abstracts

Hi Jon,

I'm putting together the latest Publications information for this week's meeting. Can you please give me an update on the papers listed below?

Thank you,

Stephanie

Stephanie Wilson Archer
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archerst@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, December 19, 2007 11:25 AM
To: Archer, Stephanie (NIH/NICHD) [E]; 'Jon Tyson (Jon.E.Tyson@uth.tmc.edu)'
Cc: 'Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu)'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN Publications | Tyson abstracts

Hi Jon,

Just following up to see if you had any updates on your papers?

Happy Holidays,

Stephanie

Stephanie Wilson Archer
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archerst@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Thursday, December 13, 2007 1:17 PM
To: Jon Tyson (Jon.E.Tyson@uth.tmc.edu)
Cc: Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu)
Subject: NRN Publications | Tyson abstracts

Hi Jon,

You had to know I was working down the list to your papers, right?

Can you tell me if these older abstracts are being prepared as papers, or should I mark them as "withdrawn" on the list?

> Tyson J, Stoll B, Ehrenkranz R, Oh W, Wright L, Stevenson D, Lemons J, Verter J for the NICHD Neonatal Research Network. Vitamin A to prevent chronic lung disease (CLD) in VLBW infants: Has the dose been too low? Pediatr Res 1994;35:321A
>
> Tyson JE, Younes N, Papile LA, Stoll BJ, Donovan EF, Bauer CR, Wright LL, Verter J for the NICHD Neonatal Research Network. Does intention-to-treat analysis (ITT) cause false-negative conclusions? Analysis of the NICHD Neonatal Research Network steroid trial (NNST). Pediatr Res 1996;39:282A

Tyson JE, Younes N, Verter J and Stevenson DK for the NICHD Neonatal Research Network. Epidemiology and ethics in developing guidelines for newborn intensive care (NIC) of extremely premature (EP) newborns (Presented at The Society for Pediatric Epidemiologic Research (SPER) Edmonton, Alberta, CANADA, June 10-11, 1997)

Tyson JE, Younes N, Verter J and Stevenson DK for the NICHD Neonatal Research Network. Value judgments and outcome assessments in developing guidelines for newborn intensive care (NIC) of extremely premature newborns. Pediatr Res 1997;41:29A

Thanks and happy holidays,

Stephanie

Stephanie Wilson Archer
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Fax: 301-496-3790
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From:	Finer, Neil
To:	Zaterka-Baxter, Kristin; M.D. Wally Carlo; Michele Walsh; Roger Faix at Utah; bradley.yoder@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Kristi Watterberg; Julie Rohr; Conra Lacy; Nancy Newman at Case; Rich, Wade
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Auman, Jeanette O.
Subject:	RE: Fi02% adjustment for altitude - revisited
Date:	Friday, January 04, 2008 4:20:45 PM

Hi Rose
At our phone call this morning we agreed that for SUPPORT, we should collect all the information required in the Physiologic Challenge and challenge all infants receiving any support as defined on Form PHY 01. The form PHY 02 requires reporting of all the details of flow and FiO2 and other support. The data could then be analyzed post hoc to determine if the infants at altitude differ in their BPD rates. It turns out that the units at altitude are challenging infants on low FiO2 with Room air as required by their payors and thus the challenge is ethically acceptable for infants on low FiO2 by cannula. This decision would not require any changes in the current forms.
The other question was related to the GDB definition of BPD which is truly a Network issue and we felt should be referred to GDB and the Steering Comm. This issue is more about how centers at altitude classify their babies by the FiO2 requirement.
I will place this issue on the Agenda for next week
Be well
Neil

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From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, November 30, 2007 12:31 PM
To: Finer, Neil; M.D. Wally Carlo; Michele Walsh; Roger Faix at Utah; bradley.yoder@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Kristi Watterberg; Julie Rohr; Conra Lacy; Nancy Newman at Case; Rich, Wade
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Auman, Jeanette O.
Subject: Fi02% adjustment for altitude - revisited

Hi all,

Please find attached modifications and additions to the BPD study regarding Fi02 adjustments at high altitude centers (Utah and NM). Dr. Yoder drafted these documents a while back and some of you may have already had discussions regarding them. The adjustments at higher altitudes will also affect Fi02 data collected for GDB and the Support study (forms NG07 and Supp05, Supp11); specific questions have been raised and are stated below:

1. Should ***actual*** Fi02 data be recorded on all forms (for Phys Def, Support and GDB)
2. If an infant is on supplemental 02 by NC at high altitude, is this infant always considered 'on-support' (see NG07 Q. 7)? If no, then what are the rules for determining when these infants are 'on-support'?
3. If an infant at high altitude is not challenged but has FiO2<.26, do we consider them ***not*** to have BPD?

4. Is <.26 the appropriate definition of room air equivalence at Utah and UNM?
5. Is a different standard going to be applied for meeting physiologic definition challenge criteria at high altitude centers? (it seems to be discrepancies between Utah and UNM)
6. If we are going to use different standards for Utah and UNM, should the attached modifications only be sent to these sites (as an ancillary component to the MOP and forms) to avoid confusion at all centers.

Please distribute comments among the group and if further discussion is necessary prior to an approval vote and consensus to these questions, we can set up a conference call.

Thanks,
Kris

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From: Das, Abhik
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT and Hot Topics presentation
Date: Friday, January 04, 2008 8:44:36 AM

I have already asked Marie to do this.

Thanks

Abhik

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 03, 2008 4:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; mcw3@cwru.edu; Wally Carlo, M.D.; bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nxs5@cwru.edu; Gantz, Marie; Das, Abhik; Poole, W. Kenneth
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: RE: SUPPORT and Hot Topics presentation

Hi Rose
As we discussed this AM, I would prefer adding PDA and NEC to our list of prospectively followed Adverse Events so that we can show appropriate concern and follow the overall occurrence of both of these.
Lets discuss at the Steering Comm.
Be well
Neil

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 03, 2008 12:45 PM
To: Finer, Neil; Rich, Wade; mcw3@cwru.edu; Wally Carlo, M.D.; bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; nxs5@cwru.edu; Gantz, Marie; Das, Abhik; poo@rti.org
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: SUPPORT and Hot Topics presentation
Importance: High

In follow-up to a presentation on oxygen saturations at Hot Topics, NICHD requests that we have some type of document available for the IRB's at our sites as the information presented at Hot Topics is relevant to the SUPPORT Study. I have attached the scanned Hot Topics presentation as well as a draft of a document for the IRB's based on the oxygen saturation information presented in the public forum

of Hot Topics. There is a rise in the rate of NEC and PDA in the Pediatrix data base after instituting new guidelines for oxygen saturation (< 28 weeks – 83-95% target) – see page 9 of the HOT TOPICS pdf file attached.

The DSMC reviewed data on NEC and PDA data are also being made available to the DSMC. At this point in time, we have been given the green light to proceed with our trial.

We may be asked by sites, families and staff the impact of the information presented on the study. I have developed a very brief description and would like input. Most sites have to report relevant findings to their IRBs during the course of clinical trials, so this document would ultimately need to go to the site IRBs. I don't think that anyone on the subcommittee was present at the presentation. We will discuss this next week at the SUPPORT subcommittee meeting. In the meantime, Please comment freely.

Thanks
Rose

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From: Finer, Neil
To: Bradley Yoder; Karen Osborne RN; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Subject: RE: SUPPORT randomization cards
Date: Thursday, January 03, 2008 7:58:15 PM

If this is categorized as a fetal death, then there is no issue and the infant would not be considered at a study patient
Neil

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Thursday, January 03, 2008 4:10 PM
To: Karen Osborne RN; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kzaterka@rti.org
Subject: RE: SUPPORT randomization cards

Sorry that I am late in the communication line on this case.
Although the randomization card was pulled in anticipation of an imminent birth....this was a fetal death....and is so being labeled by the attending MFM doc.
If we are not collecting information on fetal deaths as part of the Network GDB, we ought not to collect data on this patient either.

Brad

Brad Yoder
Dept of Peds/Neonatology
University of Utah
Phone 801-581-7052
Fax: 801-585-7395
Pager: 801-339-0092
Email: bradley.yoder@hsc.utah.edu

From: Karen Osborne RN
Sent: Thursday, January 03, 2008 5:15 PM
To: Bradley Yoder
Subject: FW: SUPPORT randomization cards

Read from the first email I sent to Kris.
Thanks!

Karen

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 3:08 PM
To: Karen Osborne RN
Cc: Das, Abhik; Gantz, Marie
Subject: FW: SUPPORT randomization cards

Hi Karen,
The consensus below is that this infant should be enrolled in Support and both the Support and GDB forms completed; please complete the Supp03 as stated below (code 2 patient died under question 9).

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 03, 2008 4:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Rich, Wade; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT randomization cards

I agree
Neil

Neil N. Finer, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 03, 2008 1:05 PM
To: Zaterka-Baxter, Kristin; Finer, Neil; Rich, Wade; Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT randomization cards

It sounds like the child met all inclusion criteria and one of the exclusion criteria. I would say that the baby is included, but mark #2 patient died under question 9 on the SUPP03 form.

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 3:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wade Rich; Das, Abhik; Gantz, Marie
Subject: FW: SUPPORT randomization cards

Hi,
Please see below for details of the Support case mentioned earlier at Utah.
Thanks,
Kris

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Thursday, January 03, 2008 3:17 PM
To: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT randomization cards

Actually what happened was the baby (b) (6) [redacted] So no apgars were assigned as it was essentially a still birth even though (b) (6) [redacted].

Does that help?

Karen

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 03, 2008 12:00 PM
To: Karen Osborne RN
Subject: RE: SUPPORT randomization cards

Hi Karen,
We need a bit more info; did the child have apgars assigned and was there resuscitation attempted?? Unless the baby was a stillbirth, he/she should be considered "enrolled." Please send as much detail as possible.
Thanks much,
Kris

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Thursday, January 03, 2008 11:37 AM
To: Zaterka-Baxter, Kristin
Subject: SUPPORT randomization cards

Hi Kris,

Happy New Year to you!

We had a baby that was delivering (b) (6) who was signed up for the SUPPORT study, but unfortunately died during delivery. The randomization card had been pulled. What is the protocol for pulled, but not used randomization cards? I can't seem to find it in the MOP although I'm sure it's in there somewhere!

Thanks!
Karen

Karen Osborne RN BSN CCRC
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Phone # (801)213-3298
Pager # (801) 339(b) (6)
Fax # (801) 587-3618

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT LONG TERM FU
Date: Wednesday, January 02, 2008 11:59:39 AM

oh boy... thanks for the heads up. Has she said yes? She has been declining new projects as she is (b) (6) . mcw

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 12/21/2007 2:54 PM
To: mcw3@cwru.edu
Subject: SUPPORT LONG TERM FU

Michele
Susan Hintz has asked Maureen Hack at Case Western to be involved with the SUPPORT long term FU given her experience with FU of cohorts of preterm infants.
The protocol just came in for protocol review subcommittee consideration – I will keep you posted.

Thanks
Rose

Rosemary D. Higgins, M.D.
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