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June 30, 2004

To Whom It May Concern:

This letter is to inform the reader about the modifications performed on the Masimo SET Radical Pulse Oximeter to be used in an NICHD Neonatal Network trial entitled " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) Trial". This study, lead by Dr. Neil Finer (UCSD) will evaluate two oxygenation ranges on infants immediately after birth and during their hospital stay. In order to mask the oxygenation ranges from the clinicians in the study, these researchers have asked Masimo Corporation to slightly alter the reading displayed on the Masimo Radical pulse oximeter between the 84% to 96% range. One group of pulse oximeters will read approximately 3% higher than the actual number while the other group of pulse oximeters will read approximately 3% low in this range. The researchers have required that the actual number be displayed below 85% and above 95%. The alarm will sound at 84% and 96%.

Masimo has performed validation tests on this software and found it works per the researchers' request. In addition, all alarms and error messages are still intact and active.

Masimo was willing to mask the pulse oximeters per the researchers' instructions since the intended ranges used in the study are in common use in Neonatal Intensive Care Units (NICUs) across the country. This study is aimed at refining the guidelines as to the best oxygen management range for neonates.

Respectfully,

Michael T. Petterson
Sr. Director, Clinical Research
Masimo Corporation

James Cronin
Vice President, Regulatory Affairs
Masimo Corporation
Irvine, CA

Infants 24 and 25 Weeks Gestational Age, Born 2001-2002
Average Days on Ventilator

CENTER	Overall		24 Weeks		25 Weeks	
	n	mean	n	mean	n	mean
Case Western	77	33.3	37	33.2	40	33.4
Texas-Dallas	62	27.1	30	27.0	32	27.3
Wayne State	57	32.0	27	32.5	30	31.5
Tennessee	5	17.0	3	18.7	2	14.5
Miami	106	29.0	58	30.9	48	26.8
Emory	81	25.6	36	25.2	45	25.9
New Mexico	2	39.5	2	39.5	0	
Cincinnati	126	26.4	68	29.5	58	22.7
Indiana	114	36.6	48	42.0	66	32.7
Yale	58	32.4	27	32.9	31	32.0
Brown	76	36.1	34	39.1	42	33.6
Stanford	38	27.1	17	21.4	21	31.7
Alabama	109	24.3	61	27.3	48	20.5
Houston	144	39.2	70	43.6	74	35.1
Duke	49	25.2	22	29.5	27	21.7
Wake Forest	92	29.2	49	28.6	43	29.8
Rochester	51	45.1	25	45.9	26	44.3
San Diego	95	21.4	45	21.7	50	21.1

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Child Health
and Human Development
Bethesda, Maryland 20892

6100 Executive Boulevard
Room 4B03B
Rockville, MD 20852

June 3, 2004

To: Cathy Spong, M.D., Pregnancy and Perinatology Branch Chief

From: Rosemary D. Higgins, M.D.
Program Scientist, Neonatal Research Network

Subject: Request for use of funds from NHLBI for capitation costs for SUPPORT Trial

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants, and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder. However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges, and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\leq$ 1 hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer

requiring ventilatory support or oxygen.

The primary hypotheses are:

1. Relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.
2. Relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

Secondary Hypotheses include:

Use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up

  A decreased incidence of cerebral palsy at 18-22 month follow-up

Infants eligible for the trial include:

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or

  Infants without known major congenital malformations

We anticipate the need to enroll 1300-1400 infants over 2-3 years with long term follow up at 18-22 months for study subjects.

Training is schedule to occur September 14-6, 2004 in Cincinnati, Ohio. This site was selected to have both protocol forms training and hands on training in the neonatal intensive care unit with the CPAP and Neopuff devices. Training costs are $3,500 per site with an addition $2,000 per site from the NICHD closeout budget. We are estimating enrollment of 43 patients in the first month of the trial. Two hundred pulse oximeters are needed for the study at a cost of $2,000 each. Additional equipment costs include Neopuff resuscitation bags and patient respiratory circuits. The total award for FY 2004 (prior to September 30) is $683,373. Attached are budget spreadsheets and IAA.

FY04 September 2004											
SUPPORT TRIAL											
	25%GDB	25%GDB							Equipment		
	est pts	est. pts	50% at	$2000/pt	Training	Subtot	Indirect	*Total*	Pulseox*	$2000 per	# of
	enrol/yr	enrol/mo	First mo			Directs	Rate	*Costs*	by size of center	Pulseox	Neopuffbag
CW	36	3	2	$4,000	$3,500	$7,500	0.53	$11,475	8	$16,000	2
TX-Dal	39	3	2	$4,000	$3,500	$7,500	0.495	$11,213	9	$18,000	2
WS	59	5	3	$6,000	$3,500	$9,500	0.56	$14,820	13	$26,000	3
MI	71	6	3	$6,000	$3,500	$9,500	0.5	$14,250	15	$30,000	4
EM	49	4	2	$4,000	$3,500	$7,500	0.515	$11,363	11	$22,000	3
CN	90	8	4	$8,000	$3,500	$11,500	0.545	$17,768	20	$40,000	4
IN	74	6	3	$6,000	$3,500	$9,500	0.53	$14,535	16	$32,000	4
YL	41	3	2	$4,000	$3,500	$7,500	0.49	$11,175	9	$18,000	2
BR	61	5	3	$6,000	$3,500	$9,500	0.299	$12,341	13	$26,000	3
ST	34	3	2	$4,000	$3,500	$7,500	0.393	$10,448	7	$14,000	2
AL	74	6	3	$6,000	$3,500	$9,500	0.6	$15,200	16	$32,000	4
TX-Hstn	83	7	4	$8,000	$3,500	$11,500	0.435	$16,503	18	$36,000	4
DU	34	3	2	$4,000	$3,500	$7,500	0.54	$11,550	7	$14,000	2
WF	69	6	3	$6,000	$3,500	$9,500	0.45	$13,775	15	$30,000	3
NY	32	3	2	$4,000	$3,500	$7,500	0.595	$11,963	7	$14,000	2
UCSD	71	6	3	$6,000	$3,500	$9,500	0.515	$14,393	16	$32,000	4
		77	43	$86,000				$212,768	200	$400,000	48
*# Pulseoxes determined by percentage of expected recruitment by center, calculated on base sheet											
**based on number of expected recruitment for entire study											

Neopuff bag	Neo circuit	*Total*	Total	
$1000 ea	$15/pt**	*equip costs*	FY04	
$2,000	$885	$18,885	$30,360	CW
$2,000	$975	$20,975	$32,188	TX-Dal
$3,000	$1,455	$30,455	$45,275	WS
$4,000	$1,740	$35,740	$49,990	MI
$3,000	$1,200	$26,200	$37,563	EM
$4,000	$2,220	$46,220	$63,988	CN
$4,000	$1,830	$37,830	$52,365	IN
$2,000	$1,020	$21,020	$32,195	YL
$3,000	$1,500	$30,500	$42,841	BR
$2,000	$840	$16,840	$27,288	ST
$4,000	$1,815	$37,815	$53,015	AL
$4,000	$2,055	$42,055	$58,558	TX-Hstn
$2,000	$840	$16,840	$28,390	DU
$3,000	$1,695	$34,695	$48,470	WF
$2,000	$795	$16,795	$28,758	NY
$4,000	$1,740	$37,740	$52,133	UCSD
$48,000	$22,605	$470,605	$683,373	

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

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0. 31	0.035-0.258
Pneumothorax	3861	0.087	0..29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0. 34	0.029-0.340
Pneumothorax	1667	0.116	0. 32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming[i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

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

The SUPPORT Trial

DATA AND SAFETY MONITORING PLANS

Adverse Events

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [i] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [ii] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Accural Reports

RTI will produce enrollment reports on a monthly basis. This report will consist of Numbers Screened, Numbers Eligible, Numbers Randomized, and Consent Status. This report can be modified as deemed necessary.

Table 1: Proportion and 2 Standard Deviations for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.014	0.850	0.108-0.371
DR Chest compressions	4050	0.108	0.010	0.621	0.035-0.258
Pneumothorax	3861	0.087	0.009	0.565	0.023-0.195
Death within first 14 days	4055	0.159	0.011	0.731	0.092-0.325

Table 2: Proportion and 2 Standard Deviations for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.023	0.938	0.153-0.520
DR Chest compressions	1805	0.133	0.016	0.679	0.029-0.340
Pneumothorax	1667	0.116	0.016	0.640	0.026-0.239
Death within first 14 days	1808	0.249	0.020	0.865	0.124-0.485

Table 3: Proportion and 2 Standard Deviations for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	2 X SE	2X SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.016	0.751	0.022-0.263
DR Chest compressions	2245	0.088	0.012	0.567	0.034-0.200
Pneumothorax	2194	0.066	0.011	0.495	0.022-0.155
Death within first 14 days	2247	0.086	0.012	0.562	0.039-0.160

Note: The sample includes infants that were born on or after Jan 1, 2002 that have reached status.

Department of Health and Human Services
National Institutes of Health
Agency Agreement and Clearance

X Intra-agency Agreement (within NIH) Inter-agency Agreement (outside NIH)	Title of the Agreement CPAP Study with NICHD

Summary of Substance of the Agreement (include purpose, resources committed: funds, personnel, equipment, facilities, etc.)
NHLBI will co-fund the Continuous Positive Airway Pressure (CPAP) and Oxygenation Trial (COT Study).

Agency Agreement Number:
Paying: Y2-HO-4049-01
Receiving: Y3-HD-4575-01

Delegations of Authority Under the Agreement
This agreement is made in accordance with

Section 301 of the Public Health Service Act, as amended (42 U.S.C. § 241)

Period of the Agreement
October 1, 2003 - September 30, 2004

Billing Information

Paying Agency NHLBI
Agency Location Code: 75080031
EIN: 152085811501
Address: Govt. Accounting Section
Building 31, Room B1B05
31 Center Dr, MSC 2045
Bethesda, MD 20892-2045

Receiving Agency NICHD
Agency Location Code: 75080031
EIN:
Address: Govt. Accounting Section
Building 31, Room B1B05
31 Center Dr., MSC 2045
Bethesda, MD 20892-2045

Accounting Information

Paying Federal Agency	Agreement Number (for NIH Y1/Y2)	Appropriation	CAN	Amount	Signatories (Name, Title)	Date
NHLBI	Y2-HO-4049-01	75-4-0872	4-8424166	$683,373	Barbara Alving Barbara Alving, M.D. Acting Director, NHLBI	5/21/04

Accounting Information

Receiving Federal Agency	Agreement Number (for NIH Y3)	Appropriation	CAN	Amount	Signatories (Name, Title)	Date
NICHD	Y3-HD-4575-01	75-4-0844	4-8421397	$683,373	[signature] Dr. Duane Alexander Director, NICHD	5/24/04
					[signature] Thomas Hooven ADA, NICHD	5/25/04

NIH Project Officer, ICD, Phone	NIH Administrative/Budget Office Contact, ICD, Phone
	Sandy Gault, Financial Management Officer, NHLBI, 6-4653

DHHS/NIH Clearances	
	ICD:
	Signature:

NIH 1742 (rev. 10/98)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

January 15, 2004

TO: Barbara Alving, M.D.
Acting Director, NHLBI
THROUGH: Director, DLD
Director, LBDP

FROM: Health Scientist Administrator, DLD

SUBJECT: Co-funding of CPAP Study with NICHD

This is a request for NHLBI to co-fund an important ventilation study initiated by the NICHD Neonatal Research Network. We are proposing that NHLBI support capitation costs for the clinical trial at a total cost of $683,373 in FY2004 and $5.1 million overall through FY2008.

Dr. Rose Higgins, the project officer for the NICHD Neonatal Research Network has solicited NHLBI co-funding for a randomized control trial: Continuous Positive Airway Pressure and Oxygenation Trial (COT Study) in extremely low birth weight infants. This study is an important attempt to evaluate CPAP (continuous positive airway pressure) intervention, as well as the use of lower SpO2 ranges in the management of this vulnerable group of infants. In order to reduce lung injury. It will begin in the delivery room and continue in the NICU, with a permissive ventilation strategy if intubation is required.

The total capitation costs of the study for NHLBI is estimated at about $5.1 million overall (Table indicates Total Costs). Although NICHD plans to conduct this study, it will necessarily be subject to prioritization among other, expensive projects, likely resulting in delay. I would recommend that NHLBI examine the fiscal possibilities for fully co-funding this study. Through the years, other studies of overlapping interest have been co-funded with the NICHD Neonatal Research Network.. For example, NHLBI co-funds the MFMU BEAM trial (antenatal magnesium and long-term neonatal outcome) through an inter-agency agreement whereby NHLBI provides the capitation costs. The STOPROP (retinopathy of prematurity) study was co-funded with NEI and a long-term study on the effect of maternal life styles on newborns has been co-funded by NIDA since 1994.

As you are probably aware, oxygenation remains the major problem in the care of infants with respiratory distress. The Columbia finding that oxygen delivery to

premature infants via nCPAP reduces the incidence of BPD has not resulted in a more universal adoption of the method, largely due to its considerable demands on NICU staff. To date, all U.S. studies with nCPAP in the group of extremely low birth weight prematures have been retrospective. It is noteworthy that an NHLBI study on the early use of nCPAP in the premature baboon model of BPD resulted in an improvement in the number and structure of alveoli. However, it has not yet been determined whether the advantaged lung status produced in the nCPAP group of baboons is due to the reduction in volutrauma or to the complete elimination (by this method of oxygen delivery) of infection and all its inflammatory consequences.

There is a resurgence of interest in nCPAP as the modality for oxygenation of premature infants, largely due to the successes reported by European institutions. The Columbia experience has never been subjected to a rigorous clinical study and that success has often been attributed to the numbers of respiratory therapists at that institution available for monitoring. Before nCPAP could be adopted as the standard of care for oxygenation of premature infants, clinicians would have to be convinced of its cost-effectiveness, assessed with reference to an optimal oxygen saturation, a reduction in the incidence of IVH and BPD, and an improvement in the over-all neurologic outcome for these infants. Therefore, the results of the NICHD study on nCPAP and oxygenation will provide extremely useful information with broad influence on the clinical management of this group of babies.

The COT Trial is a prospective, blinded, randomized, 2X2 factorial design which will test the individual factors of lower oxygen levels and volutrauma reduction via nCPAP oxygen delivery. There will be two randomization strata: infants of 24-25 weeks and infants of 26-27 weeks, in order to appropriately distribute risk among the four arms, since the study will not be powered to detect outcome differences between strata with significance. The number of subjects is 1300-1400 babies and recruitment is expected to require about 2-3 years.

A new device, the Neopuff, will be used in this study. It allows for the accurate delivery of a pre-determined O2 pressure via nCPAP or endotracheal tube, with very little intra-individual variation, even among those not necessarily trained as respiratory therapists. This development relieves a major impediment to comparing the use of CPAP with the more common modalities of ventilation used in the U.S., where the standard devices in use in delivery rooms often result in overshooting PIP.

I think that this study has the possibility for making a beneficial adjustment in the clinical care of low birth weight premature infants, whose numbers continue to increase. BPD is acknowledged to be a developmental disorder of multifactorial origin, such that no single "magic bullet" is expected to prevent it. However, the evidence indicates that the mode of oxygen delivery is responsible for the first *ex utero* insult to the underdeveloped lung.

NHLBI participation in the COT Trial would indicate that cooperation between NHLBI and NICHD is based upon a shared responsibility to improve the standard of clinical care for this ever-increasing group of extremely low birth weight premature infants. The need to provide appropriate O2 assistance to the developing lung evolves from many of the basic studies supported by NHLBI. Moreover, exploring methods for appropriate pulmonary management of infants, as well as adults, would appear to be a direct responsibility of NHLBI.

Mary Anne Berberich

Mary Anne Berberich, Ph.D.

COT STUDY (TOTAL COSTS)

Project Year	01	02	03	04	05
Fiscal Year	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008
Capitation Costs	$683,373	$2,749,282	$1,334,919	$329,648	$27,440
NRN Base Costs	$3,914,000	$4,031,420	$4,152,327	$4,278,072	$4,406,414

Attachments: Study Protocol
Budget

☑ Approve ☐ Do not Approve

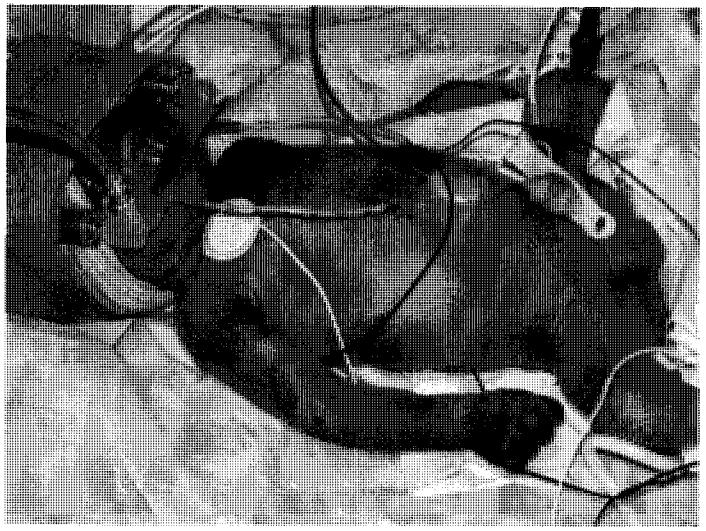
Barbara Alving

Barbara Alving, M.D.

1/30/04

Date

cc: Sandra Gault

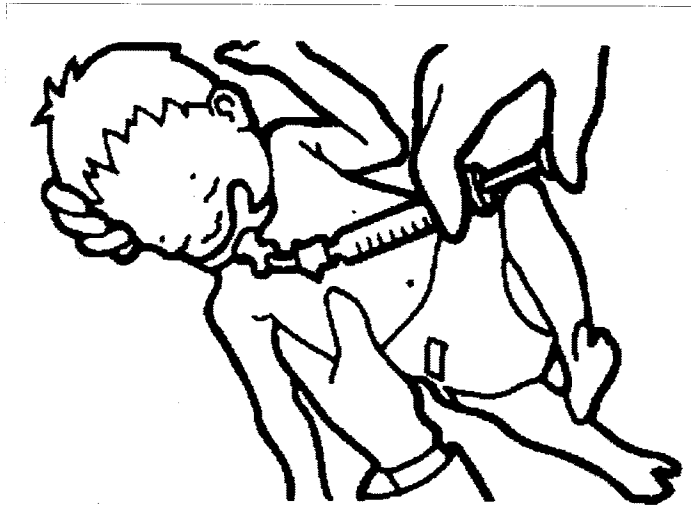


SUPPORT TRIAL

Rationale

Evidence

Protocol



Evidence for Efficacy of CPAP

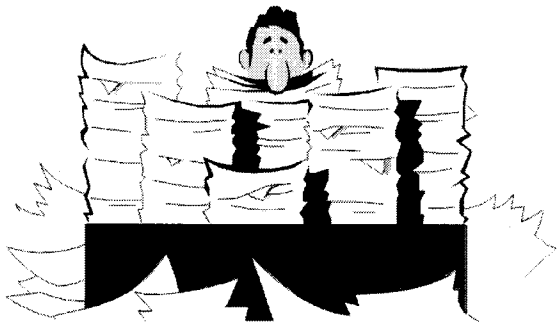
- Gregory et al (NEJM 1971;284:1330) demonstrated that CPAP improved oxygenation in infants < 1500 gm with RDS
- Rhodes et al (Pediatr 1973;52:17) reported increase survival with face mask CPAP
- CPAP improves FRC and premature infants without adequate FRC are more likely to develop HMD (Upton et al, Arch Dis Child 1991;66:39)
- The use of CPAP decreases mortality in the presurfactant era (Ho et al Cochrane LibraryCLIB Issue #3 2002)

Evidence for Efficacy of CPAP: Population – European VLBW Cohort Studies

- Jonsson et al (Acta Pediatr 1997;419:4) reported experience from Stockholm from 1988 – 1993 and use of higher $PaCO_2$ 51% treated with early CPAP < 30 min usually, only 1/3 required intubation
- ✓ Almost all infants < 24 weeks required intubation
- Gitterman et al (Eur J Pediatr 1997;156:384) reported that CPAP usually within 15 min of birth, reduced the need for intubation mortality, and LOS
- Poets et al (Pediatr 1996;98:24) reported ↓ ventilation, without increased BPD, IVH or PVL in Germany from 1992-1994

Evidence for Efficacy of CPAP: Last Pre-Surfactant Prospective Trial Han et al Early Human Dev 1987;15:21

- Compared early CPAP (up to 2hours after birth)
- ☹ No maternal Antenatal Steroids
- ☹ CPAP associated with worse oxygenation
- ✘ There is no Post-Surfactant Antenatal Steroid Era prospective RCT comparing DR/Early Surfactant to Surfactant
- ✘ Current Cochrane Review on Prophylactic CPAP concludes that a multicentered RCT comparing prophylactic CPAP with standardized care was needed! (Subramanian et al Cochrane Library Issue4 2003)



Origins of Chronic Lung Disease

- **Review of number of units demonstrated that the unit which used least ventilation, allowed permissive hypercarbia and used initial Nasal CPAP had lowest BPD rates (Columbia)**
- **This unit did not use muscle paralysis**
- **Recently reported low BPD rate = 3/81, (4.7%)**
- **50% survival without BPD for infants 500-750 gm**

Avery et al, Pediatr 1987:79:26

Interhospital Variation of Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

- **Compared early ventilatory practices for VLBW infants at 2 Boston Hospitals (341 infants) with Columbia (100 infants) born from 1991 to 1993**
- **They evaluated use of mechanical ventilation for days 1-3, and 4-7**

❁ ***CLD (O_2 at 36 weeks) was 4% (Babies) vs 22%(Boston)***

❁ **No differences in IVH, PVL, NEC, ROP, or mortality (9% vs 10%)**

Interhospital Variation of Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

Other practices: Babies vs Boston

- ✓ **Surfactant 10% vs 45% more often in CLD, 23% vs 65%**
- ✓ ***CPAP used primarily at Babies 63% vs 11%***
- ✓ ***Mechanical Ventilation as primary 29% vs 75%***
- ✓ **Infants with CLD more likely to receive Mechanical Ventilation 77% vs 42%**
- ✓ **Duration of Mechanical Ventilation 13 days vs 27 days**
- ✓ **$PaCO_2$ higher at Babies**

Mechanical Ventilation and Chronic Lung Disease:
Van Marter et al Pediatr 2000;105:1194

- **Overall Odds Ratio for the development of CLD was related to need for Mechanical Ventilation**
- **on day of birth - OR = 13.4**
- **Days 1 - 3 - OR = 9.6**
- **Days 4 -7 -OR = 6.3**
- **Maximum PIP of > 25 cmH_2O at birth, or > 20 cmH_2O at 1 -3 days increases risk for CLD**
- ***Message: If you don't intubate, the babies do better!!!***
- ***Oh by the way, this is all retrospective information!!!***

Mechanical Ventilation and Chronic Lung Disease:
Serenius et al Acta Paediatrica. 2004; 93(8):1090-1097

- **Other studies have reported association between duration of ventilation and BPD/CLD**
- **BPD was associated with duration of mechanical ventilation (OR 2.71 per 1-wk increment in duration; 95% CI 1.76-4.18)**
- **Other morbidities associated with ventilation**
- **Severe IVH or PVL was associated with duration of mechanical ventilation (OR 1.53 per 1-wk increment in duration; 95% CI 1.01-2.33)**

Nasal CPAP and Early Surfactant for < 30 wk Infants:

Verder et al, Pediatr 1999;103(2).

- **11 Neonatal Units in Denmark from April 1995 to Jan 1997**
- **Previous study (NEJM 1994;331:1051) showed benefit for early CPAP (not DR) followed by intub + Surf + extubation**
- **Infants < 30 wks, + RDS, a/APO_2 was .35-.22 on CPAP $\geq$ 6 cmH_2O**
- **<u>Treated with early CPAP and given Surfactant</u>**
- **Randomized to :early Curosurf vs later when a/APO_2 < .21-.15**
- **Infants intubated for Curosurf 2.5ml/kg in 2 doses,**

  then extubated, usually within 10 minutes!!!

Verder et al, Pediatr 1999;103(2).

Results: BW=950gm vs 935, Gest=27 vs 28, Nasal CPAP started at median of 17 minutes

→Randomization at 4.3 hours

→Early Rx rec'd Surfactant at 5.2 hrs vs 9.9 hrs for late group

→Only 4 infants could not be extubated after Surfactant instillation

→MVent/Death = 21% vs 63%, p=0.0013 by logistic regression

→Death = 9% for Early Rx vs 26% for late Rx

Evidence for Efficacy of DR CPAP: Lindner et al, Pediatr 1999;103:961

- Evaluated prolonged inflation (20-25 cm H2O for 15 secs) followed by CPAP
- Accepted high PaCO2 >70 torr and FiO2 > .6
- Reported a reduction in intubation from 84% in 1994 to 40% in 1996
- No difference in mortality, IVH,BPD and no airleaks on admission to NICU

Evidence for Early CPAP: Recent Cohort Studies

- De Klerk and de Klerk (J Pediatr Child Health) 2001;37:161) used CPAP within 10 minutes of birth for infants 1000-1500 gm
- Reported decreased intubation, surfactant use, and ventilation duration and oxygen at 28 days.

Evidence for Early CPAP:
Sandri et al, Ped Res 2001;49:273A
Thomson et al, Ped Res 2002;45:321A

- Sandri et al -155 infants 28-31 weeks CPAP < 30 min age or if FiO2 >.4
- No differences for surfactant use or ventilator
- Thomson et al, 237 27-29 week infants - 4 arms – CPAP + Rescue surf, Surf followed by Surf, Early IPPV + Surf, Conventional Management
- CPAP began < 6 hours in 76-79% - not DR, not really early
- No differences for CLD
- These are most recent studies

Early CPAP in the ELBW Infant

Narendran et al, J Perinatol 2003;23:195

- **Evaluated infants 401-1000 gm and compared historical cohort N=92, with Bubble CPAP initiated in DR, N=79**
- **Gest = 26 weeks, BW = 760 gm**
- **Reported decreases for:**

✓ **DR Intubations - 60% versus 32%**

✓ **Duration of Mech Ventilation – 28 versus 13**

✓ **Use of Post Natal Steroids – 42% versus 14%**

Early CPAP vs Mechanical Ventilation
Recent Trials

- In a study of infants < 28 wks in France, 40 received DR CPAP, 20 (50%) subsequently intubated (Boubred et al PAS 2004)
- Dani et al, (Pediatr 2004;113:E560)
- 27 infants < 6 hrs age, < 30 wks on CPAP (started at 35 min) and FiO2 > .3
- Intubated for curosurf, then randomized to CPAP within 5 min (13) vs MVent (14)
- CPAP infants req'd less ventil, oxygen and surfactant and had shorter LOS.

Early CPAP as Support for ELBW
"Columbia Approach, A Sirens Song?"

- **We have been seduced into believing that we can avoid intubating ELBW infants by observations presented by many about a few who never published anything prospective about their own practice!!**
- **Much speculation that infants < 700 gm can be managed without intubation**
- **This approach has *Never* been shown to produce good outcomes by any prospective trial**
- **Most current studies have excluded infants < 25 weeks**

DR CPAP Trial
NICHD Neonatal Network, Pediatrics, In Press

- **The Network (5 Centers) evaluated a prospective protocol which compared CPAP started at delivery versus the usual approach without DR CPAP**
- ***No infant could be intubated exclusively for surfactant in the DR***
- **All Infants were 28 weeks or less**
- **Intubated and received surfactant in NICU for minimal criteria:**

FiO2 > 0.3 to maintain SaO_2 > 90% or PaO_2 > 45 torr

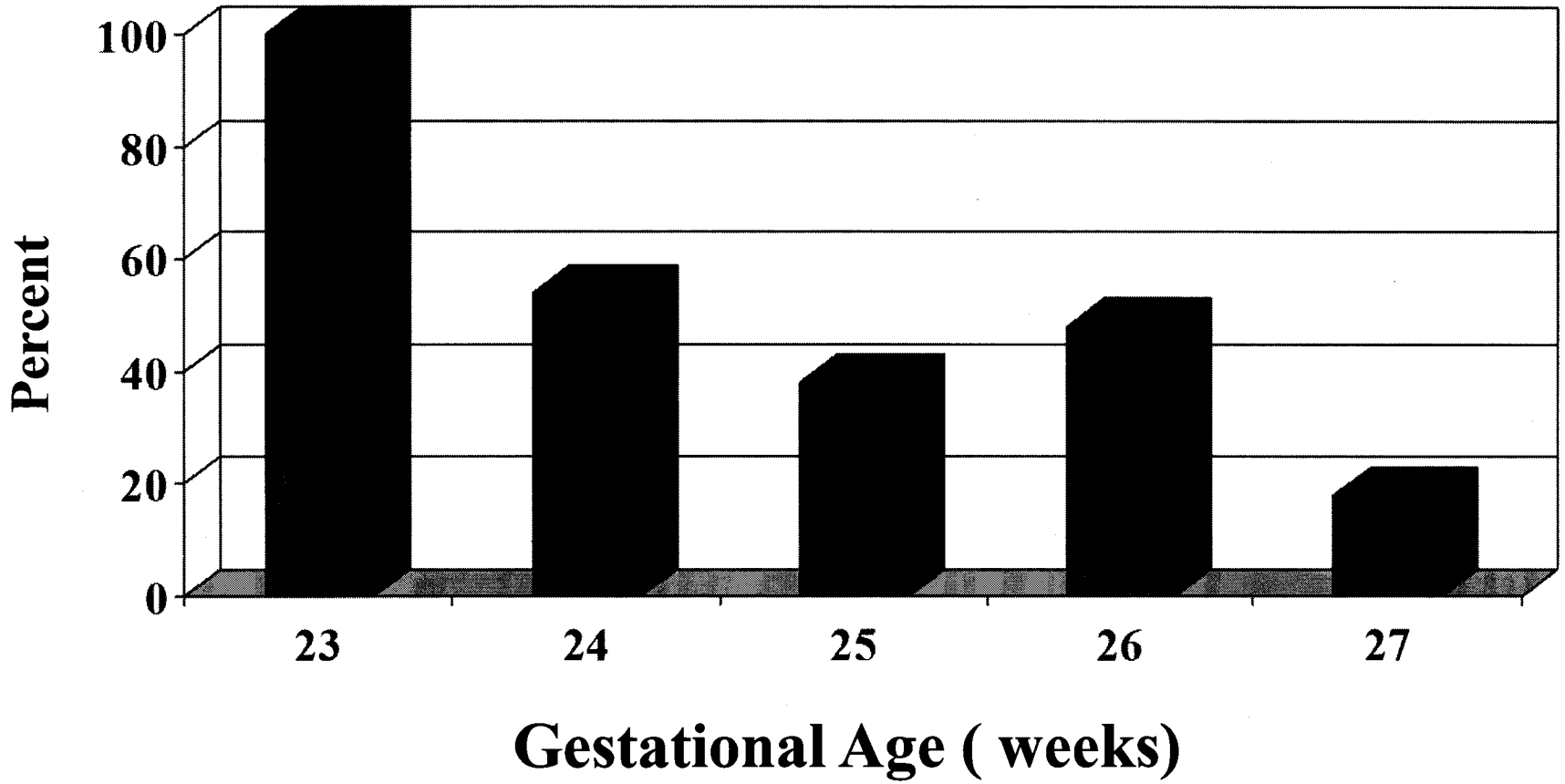
Arterial $PaCO_2$ > 55-60 with pH < 7.25

Apnea requiring bag and mask ventilation

Patient Population
Means ± Standard Deviation

	CPAP N=55	Control N=48
Birth Weight	753 ± 196	799 ± 186
Gestation (weeks)	25 ± 1.3	25 ± 1.2
Apgar @ 1 min	4	4
Apgar @ 5 min	6	6
Apgar @ 10 min	6	6

Percent Intubated in DR by Gestational Age



Conclusions from DR- CPAP Trial

- ✓ ***All Infants < 24 weeks required DR Intubation for resuscitation!***
- ✓ **Early CPAP in the DR is a feasible intervention for infants > 24 weeks and > 500 gm**
- ✓ **It is possible to provide CPAP as a randomized intervention in the DR for the ELBW Infant**

CPAP vs Mechanical Ventilation from Birth
Beneficial Effects: Animal Studies

- **CPAP from birth in preterm lambs produces gas exchange similar to or better than mechanical ventilation for 72 hours (Null et al, PAS May 2004)**
- **Preterm lambs treated with CPAP from birth at 2 hours had lungs with greater volumes and lesser neutrophils and hydrogen peroxide than lambs ventilated from birth (Jobe et al, Ped Res 2002:52:387)**

Potential Benefits of Early CPAP
Avoid Volutrauma and Hypocarbia

Bjorklund et al, Pediatric Research. 1997 ;42(3):

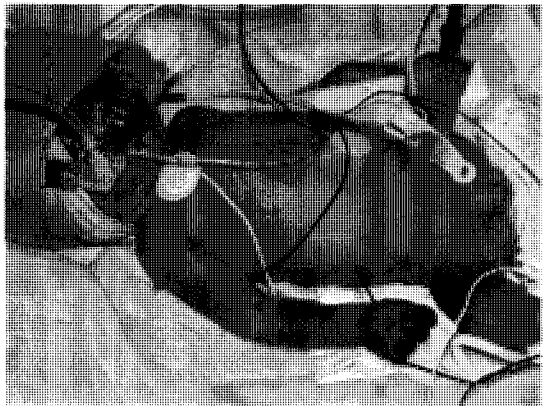
- ✓ **Five pairs of lamb siblings were delivered by cesarean section at 127-128 d of gestation. One lamb in each pair was randomly selected to receive six manual inflations of 35-40 mL/kg prior to surfactant Rx**
- ✗ **Large breaths inhibited surfactant induced increase in compliance and lung volume, and caused more lung injury**
- ✗ **"a few inflations with volumes that are probably harmless in other circumstances might, when forced into the surfactant-deficient lung immediately at birth, compromise the effect of subsequent surfactant rescue treatment."**

What Type of CPAP- Does it Matter?

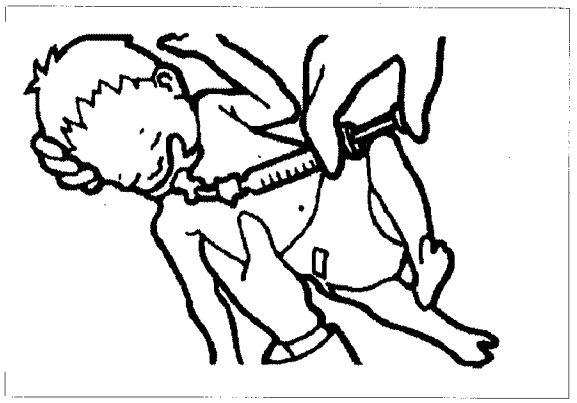
- **No data to date suggests that one form of CPAP is clinically better than another – Bubble vs Conventional**
- **Variable flow CPAP associated with lower work of breathing and improved compliance, but no effect on FRC and no clinical advantages detected (Pandit et al, Pediatr 2001, Courtney et al, Pediatr 2001, PAS 2004, Stefanscu et al Pediatr 2003, McEvoy et al PAS 2004)**
- **High Frequency CPAP used in 132 day old lambs for 72 hours compared with CMV resulted in better oxygenation over time, with no significant differences in $PaCO_2$ (Null et al, PAS May 2004)**

How Much CPAP??
Animal and Infant Studies

- ✓ CPAP of 8 cmH_2O vs 5 cm H_2O for 6 hours produces better oxygenation than Mechanical ventilation and improves fluid clearance (Mulrooney et al PAS, May 2004)
- ✓ Increasing CPAP improves oxygenation but > 8 cm H_2O may increase air leaks (Probyn et al, Ped Res In Press)
- ✓ Increasing CPAP increases lung volume in preterms, more so with variable flow CPAP (Pandit et al Pediatr 2001)



Surfactant versus CPAP



- The current dilemma is that there is an increasing interest in using early CPAP but the best available evidence indicates that intubation and prophylactic/early surfactant produces the best outcomes
- Unfortunately, there are no prospective randomized trials comparing these approaches, especially in the ELBW Infant!!

CPAP Physiologic Effects
May Offset Surfactant Benefit!!

- ☑ Decreases the work of breathing,
- ☑ Establishes and maintain an adequate functional residual capacity,
- ☑ Stabilizes air space, and promotes the release of surfactant stores.
- ☑ Avoiding endotracheal intubation is of benefit for mucociliary transport and humidification of inspired air, as well as decreasing the risk of airway damage and secondary infection and the occurrence of lung barotrauma and volutrauma secondary to MV

Comparison of Early CPAP to Surfactant: Current Studies

- ✓ **COIN trial – enrolling spontaneously breathing infants of $\geq$ 25 weeks to 28 6/7ths weeks – DR CPAP (single nasal prong) vs IPPV +Surfactant**
- ✓ **VON - 3 arms, Early Surf + Vent, Early Surf + Early extubation, Early CPAP + Selective Intubation – All infants > 25 weeks Gestation**

Comparison of Early Surfactant with CPAP

- ✘ No study to date has addressed the most vulnerable population of infants of 24 weeks where survival is now > 50%
- ✓ NICHD Neonatal Network *SUPPORT* trial will compare Prophylactic/Early Surfactant (< 1 hour) to CPAP initiated at birth
- ✓ 2 Strata – 24 to 25 6/7wks and 26 to 27 6/7 wks
- ✓ Will evaluate Neonatal Survival without ROP, BPD and Neurodevelopmental Impairment at 2 years

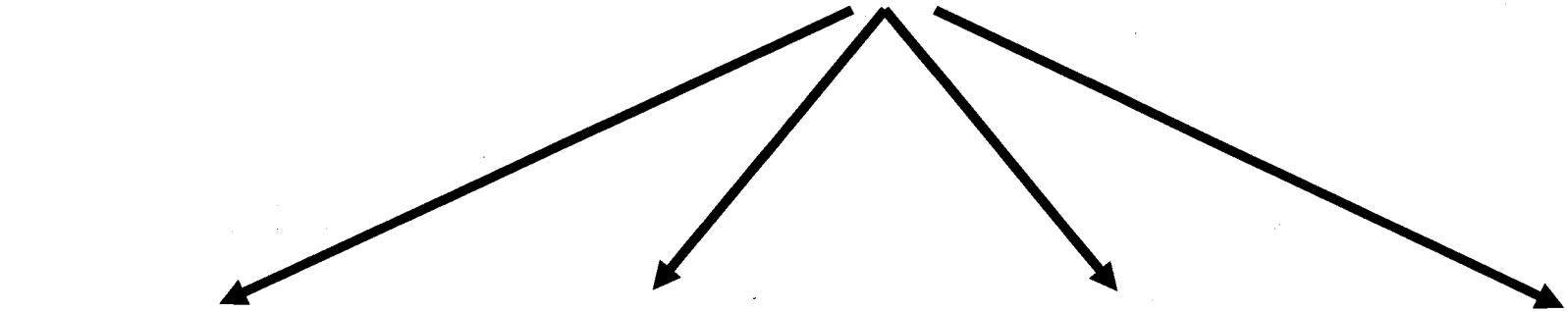
Next Trial : SUPPORT

- Surfactant
- Positive airway pressure
- Pulse Oximetry
- Randomized
- Trial

SUPPORT Trial

- **Essentially 2 trials conducted simultaneously on the same population of ELBW infants**
- **A Factorial design which ensures that there will be an equal number of infants randomized to each of the 4 possible strategies**
- **Not prospectively powered to evaluate an interaction, but if a large interaction exists, it will be noted**

Overall Study Design



We hypothesize that that the use of CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without CLD at 36 weeks.

We hypothesize that the use of a lower SaO2 range (85% to 89%) will result in an increase in survival without the occurrence of ROP or occurrence of threshold ROP and/or the need for surgical intervention.

We hypothesize that the combination of early CPAP and a permissive ventilator strategy with a lower SaO2 range will result in increased long term survival without severe developmental impairment as assessed at 18-22 months corrected age.

SUPPORT Trial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Early CPAP With Permissive Ventilation	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control with Prophylactic Surfactant	Control + Low SpO2	Control + High SpO2

PRIMARY HYPOTHESIS

- **EARLY CPAP AND PERMISSIVE VENTILATORY STRATEGY WILL INCREASE SURVIVAL OF ELBW INFANTS WITHOUT BPD**

- **LOWER SpO2 (85-89%) WILL INCREASE SURVIVAL WITHOUT SEVERE ROP (THRESHOLD DISEASE OR REQUIRING SURGERY)**

Methods: CPAP/Permissive Ventilatory Strategy

- DR management guidelines
- Intubation criteria
- Extubation criteria
- Re-intubation criteria

SUPPORT Trial: Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

SUPPORT Trial: Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available.
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

SUPPORT - Ventilation Arm

- **Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic/early surfactant within 1 hour of delivery**

SUPPORT TRIAL

Ventilation Strategies - First Hour

Treatment Arm

DR CPAP

Control Arm

Intubation and Early Surfactant < 1 hr

SUPPORT TRIAL
Ventilation Strategies - NICU

Treatment CPAP Arm

Intubation Criteria – Intubation is *Not Mandatory* for CPAP infants

May intubate CPAP Infants for Any of

FiO_2 >.50 for $SpO_2 \leq 88\%$
$PaCO_2$ > 65 torr
Hemodynamic instability

SUPPORT TRIAL
Extubation for TREATMENT - CPAP Infants

Must *Extubate* within 24 hrs of all criteria being met

$PaCO_2$ < 65 torr and pH < 7.20
SpO2 ≥ 88%nwith FiO2 < .50
FiO_2 ≥ .40 for SpO2 ≤ 88%
MAP < 10 cmH_20 Rate < 15 bpm
Amp < 2X MAP if on HFV
Hemodynamically Stable

Criteria apply for first 14 days of life

UNITED STATES OF AMERICA

SUPPORT TRIAL

Ventilation Strategies - NICU

↓

Control Surfactant Arm

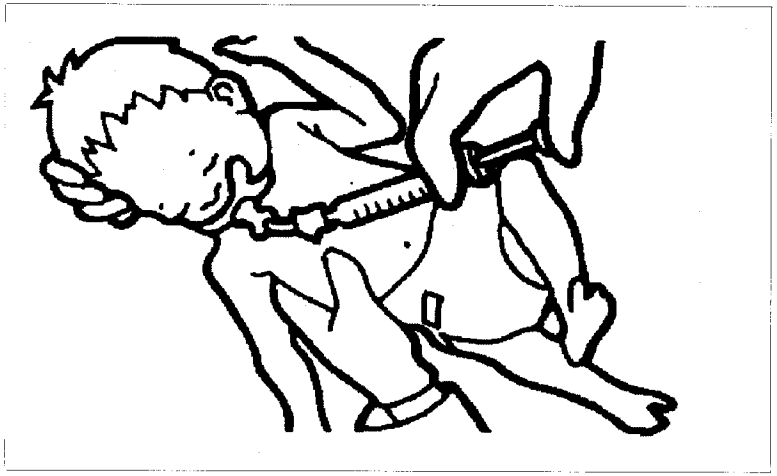
Extubation REQUIRED within 24 hrs of meeting all Criteria:

- **$FiO_2 < .35$ for $SpO_2 \geq 88\%$**

$pH \geq 7.30$ and $PaCO_2 < 50$ torr
MAP < 8 cm H_2O, Rate $\leq$ 15 bpm,
If HiFi, Amplitude < 2X MAP
Hemodynamically stable
No significant PDA

SUPPORT TRIAL

Re-intubation Criteria - Control - Surfactant



Once extubated, a Control – Surfactant infant may be re-intubated following current Standard of Care

SUPPORT - Ventilation Arm

- Treatment infants will be forced to early extubation attempt at higher ventilation settings
- Control infants will be extubated at more conventional settings
- Spontaneous extubation will not require mandatory re-intubation, unless intubation criteria are met.
- Intubation may be performed at any time for apnea, sepsis, shock or surgery

Ventilation Criteria

- **In effect for 14 days for all study infants**
- **CPAP may be discontinued when in room air > 1 hour**
- **May be restarted at any time in either group**
- **Nasal SIMV to be used *only* after initial intubation**

Oximetry Arm: Justification

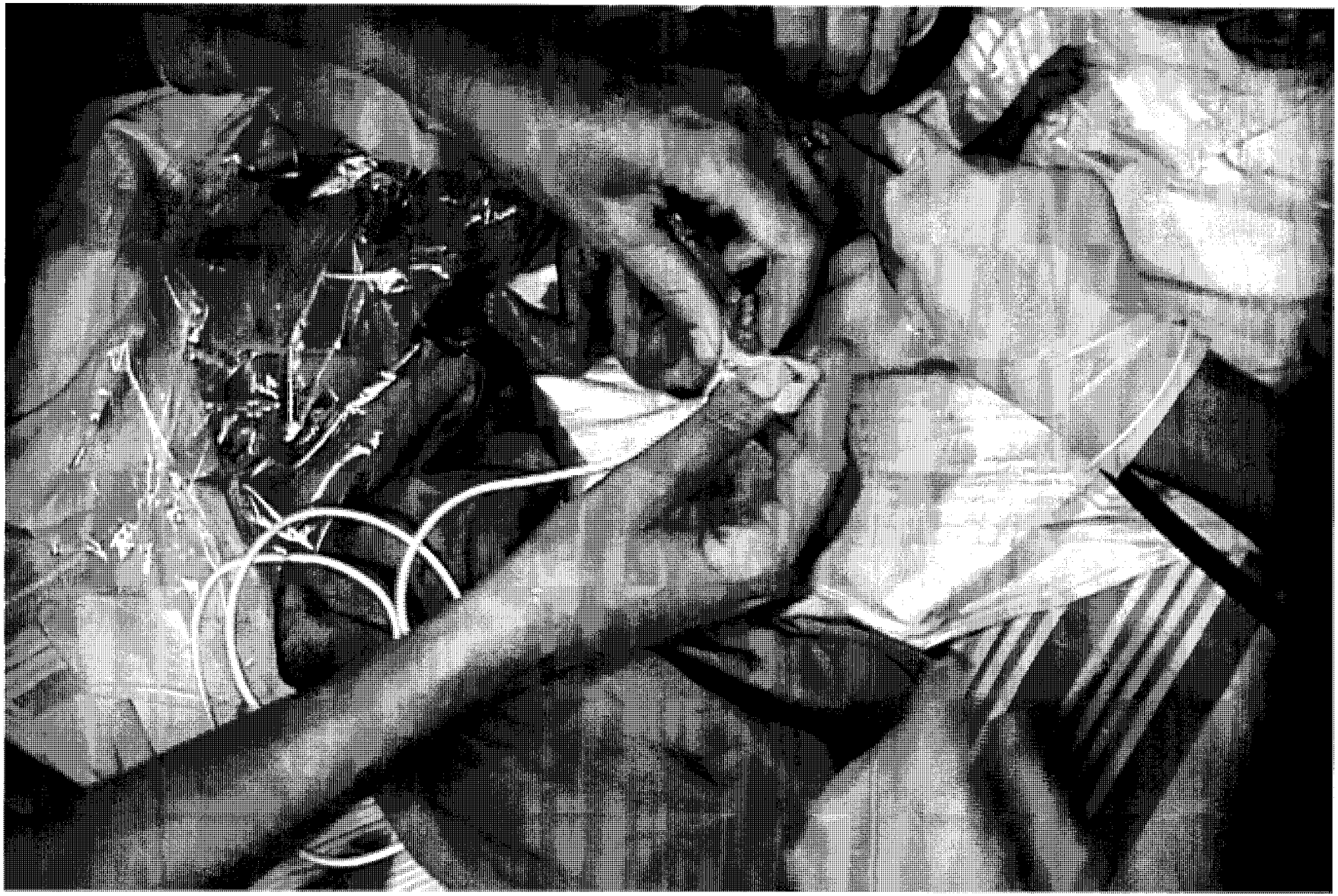
- There are major questions regarding the appropriate level of oxygen exposure during the acute management of the ELBW infant
- Retrospective data suggests that infants maintained SpO2 values of 88% to 98% had 4 times the incidence of ROP as infants managed with lower SpO2 values - as low as 70% (Tin et al, Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.)

Oximetry Arm: Justification

- Chow et al at Cedars in LA adopted an approach which involved a number of interventions including less oxygen during resuscitation, and a subsequent SpO2 range of 85% to 93% for infants < 32
- They reported a significant decrease in ROP Grades 3 to 4 from 12.5% in 1997 to 2.5% in 2001 and ROP laser treatment from 4.5% in 1997 to 0% in the last 3 years of this intervention (Pediatr 2003; 111(2):339-345)

Oximetry Arm

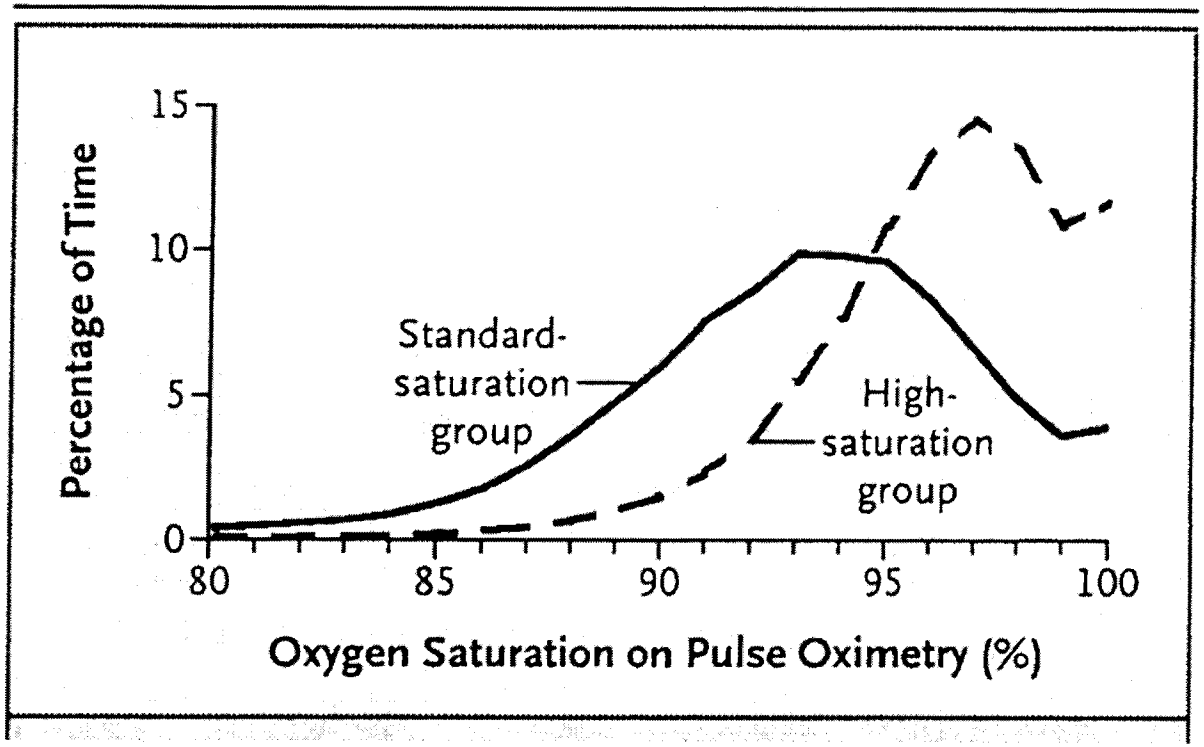
- No other trial has prospectively evaluated the SpO2 level from birth onwards
- BOOST and STOP-ROP began when infants were $\geq$ 32 weeks of age
- They used ranges of 91-94% and 95-98%
- They both reported more pulmonary morbidity and a longer need for oxygen in their high saturation group where SpO2 was $\geq$ 95%
- Our study will keep SpO2 $\leq$ 95% for both groups



BOOST Trial
Askie et al, NEJM 2003;349;959

- BOOST used a 2% adjustment in the SpO2 reading
- Low range infants read 2% lower than actual and hi range infants read 2% higher throughout the entire SpO2 range.
- Target range was 93 – 96%

SpO2 from BOOST Trial
Askie et al NEJM 2003;349:959-67



Methods: Oxygen Saturation Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter < 2 hours

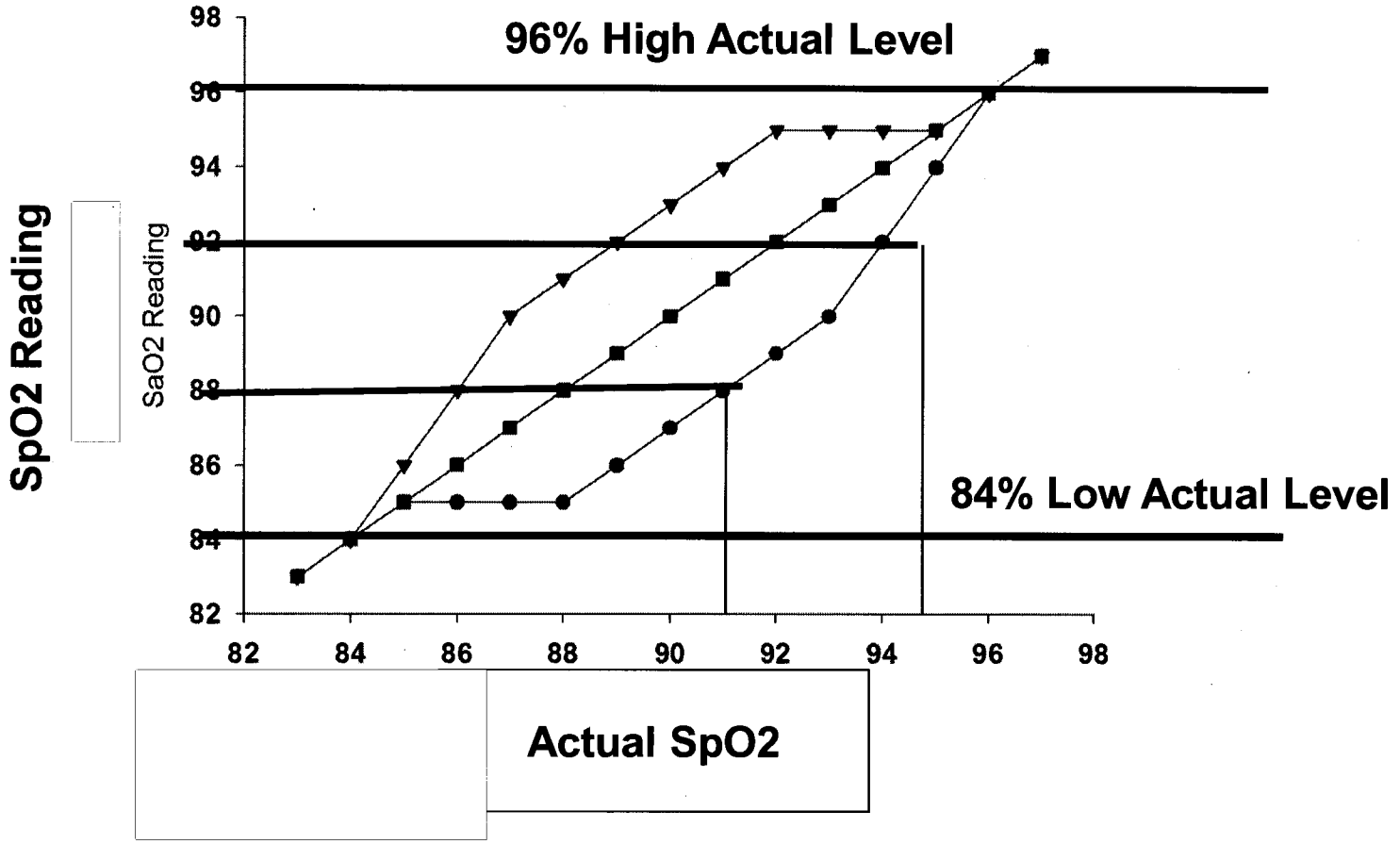
Maintain till off ventilatory support and oxygen

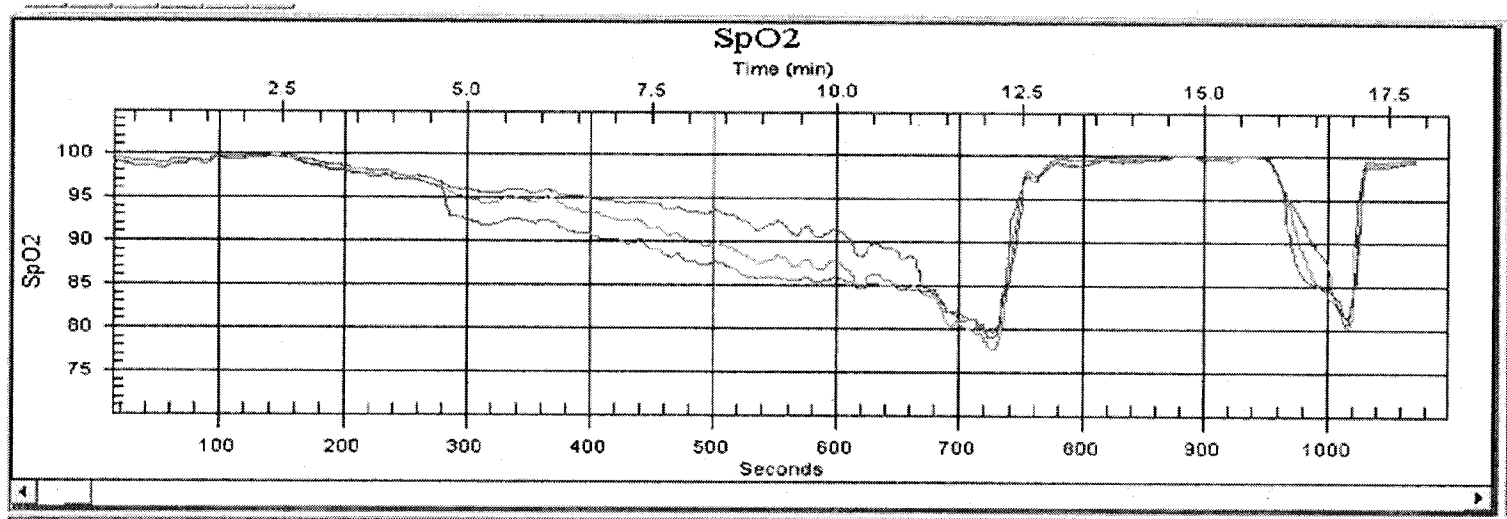
RANDOMIZATION	Displayed Target Range	Actual Range
Low SpO_2 range group	88-92%	85-89%
High SpO_2 range group	88-92%	91-95%

Pulse Oximetry Protocol

- **LOW RANGE: TARGET SpO2 85-89%**
- **HIGH RANGE: TARGET SpO2 91-95%**
- **STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE**
- **STUDY PO'S READING NOT THE ACTUAL SpO2 for READINGS BETWEEN 85% TO 95% FOR BLINDING**

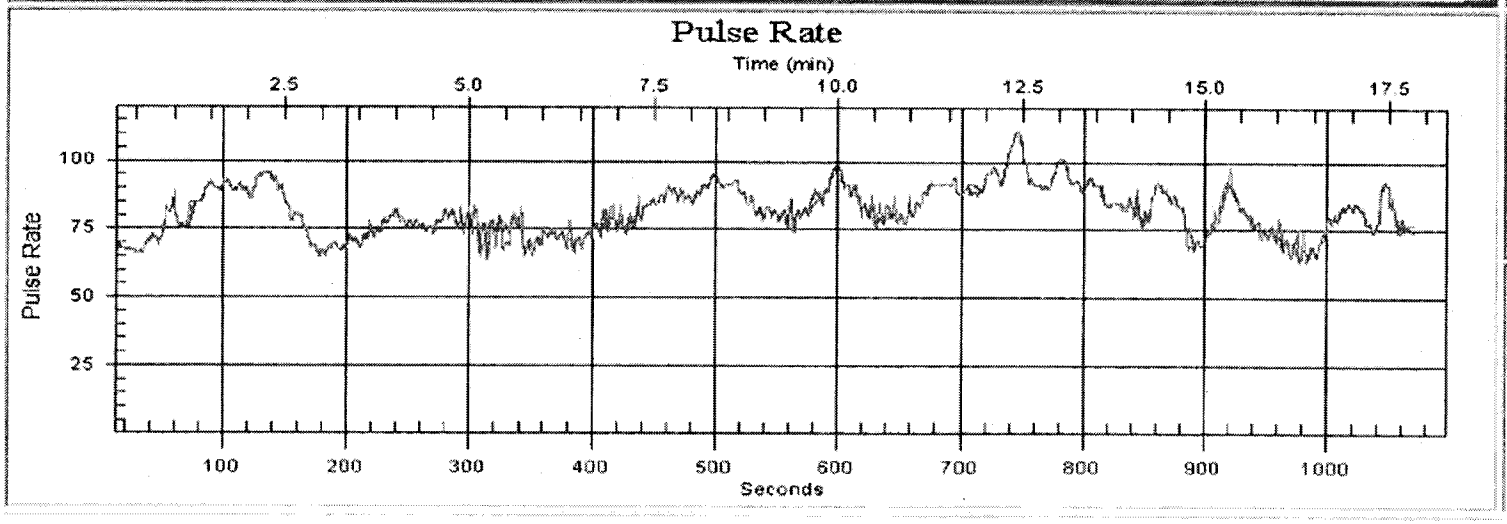
Plot of Actual versus Displayed SpO2





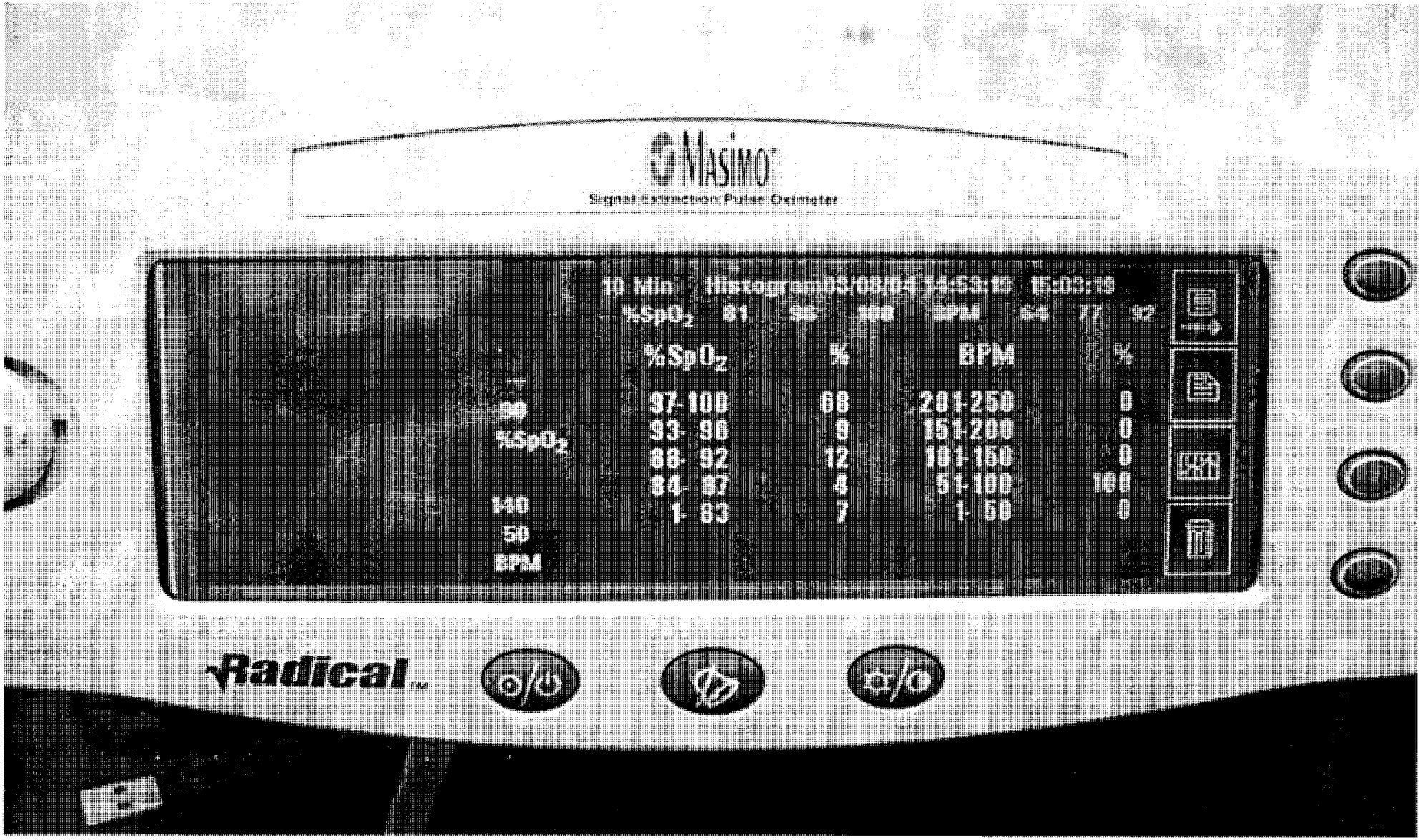
SpO2 Instruments:
REF Radical: SpO2
Low Group : SpO2
High Group : SpO2

SpO2 Comment:

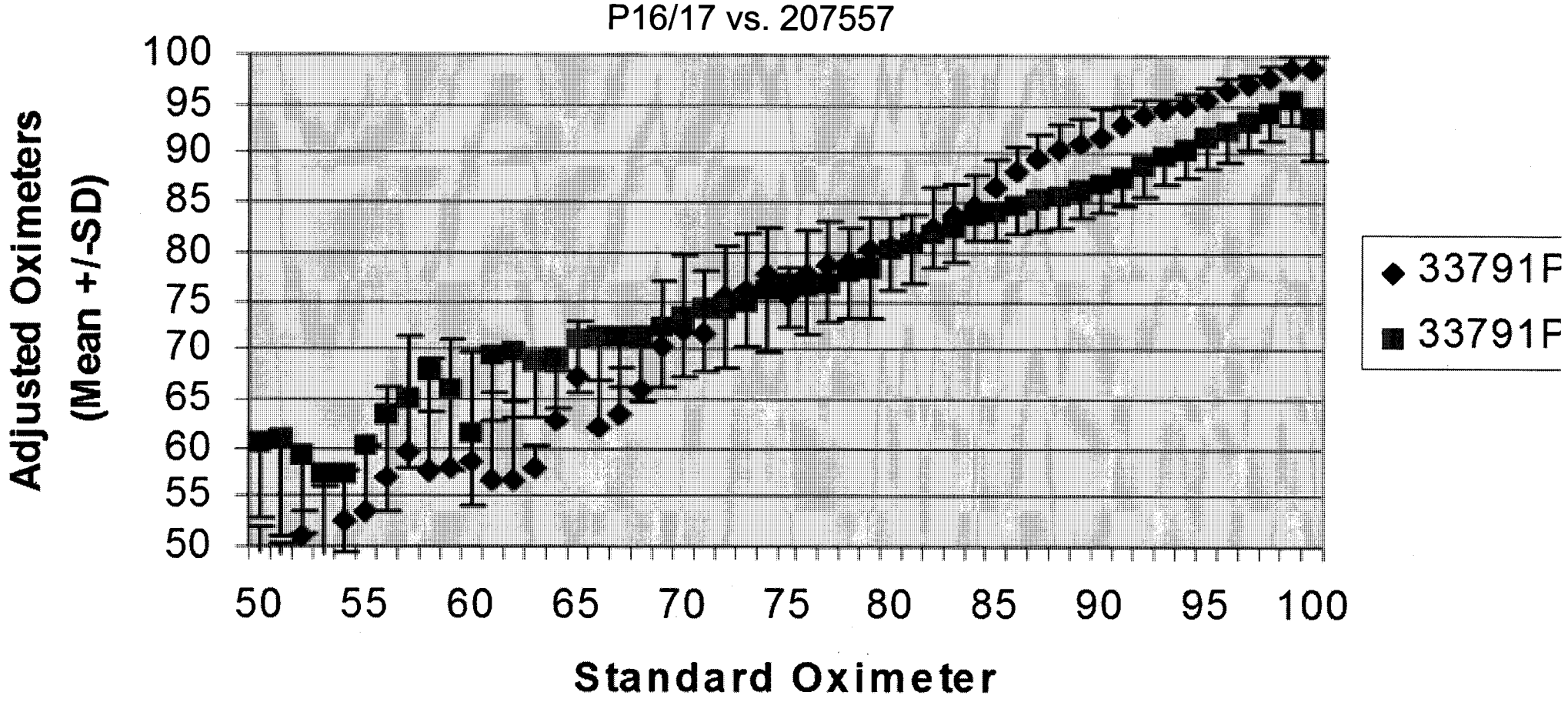


Pulse Rate Instruments:
REF Radical: PR
Low Group : PR
High Group : PR

Pulse Rate Comment:

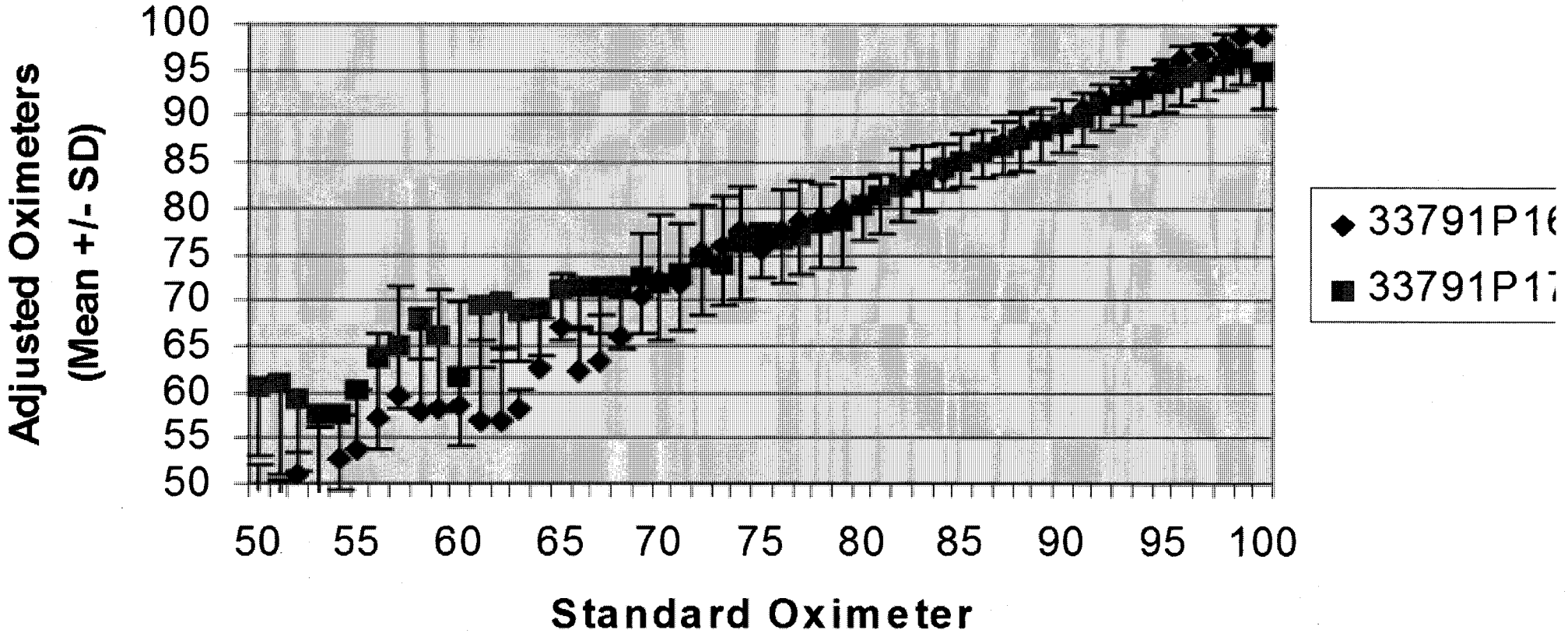

MASIMO
Signal Extraction Pulse Oximeter
10 Min Histogram 03/08/04 14:53:19 15:03:19
%SpO2 81 96 100 BPM 64 77 92
%SpO2 % BPM %
97-100 68 201-250 0
93- 96 9 151-200 0
88- 92 12 101-150 0
84- 87 4 51-100 100
1- 83 7 1- 50 0
90
%SpO2
140
50
BPM
Radical

33791 New
2 Second Resolution



33791 New
Corrected Data
2 Second Resolution

P16/17 vs. 207557



Pulse Oximetry Protocol

- **BOTH GROUPS WILL MAINTAIN DISPLAYED SATURATION AT 88-92%**
- **ALARMS FOR BOTH GROUPS WILL BE:**

  LOW – 84% HIGH - 96%

  (***Note Masimo alarms at actual limit set point, not one below*****)**
- **SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED**

OXYGENATION PROTOCOL-CONT'D

- **STUDY PO WILL REMAIN WITH INFANT UNTIL OFF OXYGEN or INFANT 36 WEEKS PCA whichever is sooner**
- **SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER MONTH - every 4 WEEKS DURING STUDY**
- **This will contain 1 data point for SpO2 and heart rate for every 10 seconds of this 1 month interval**

Sample Size Estimate

- **The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.**
- **We will randomize by family, all multiples to same arm – we have made a 12% adjustment to sample size to account for this clustering.**

Sample Size

- **Postulating a 10% difference in primary outcome a sample size of 1310 infants will provide for 80% power for the primary as well as NDI/Mortality (Secondary Outcome)**
- **This includes a 17% attrition factor**

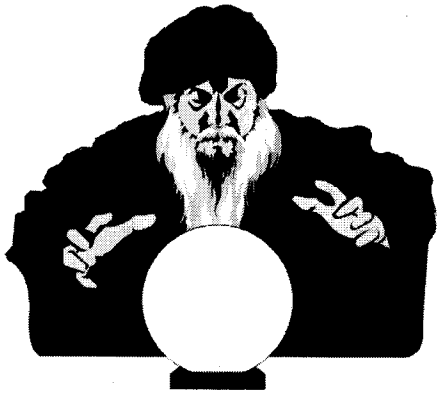
SUPPORT – Time Line

- Testing POs at Vent sites
- Study Manual available
- Oximeters to be purchased by sites
- Start Enrollment following training session
- Site visits as requested to follow Training sessions

Safety Monitoring

- **We are going to monitor the occurrence of Grade 3 and 4 IVH, air leaks on admission or in the first 14 days, the need for compressions or epinephrine in the DR and death during the trial. If these occurrences are greater in any arm(s) of the trial, this information will be available to the DSMC (which has been expanded for this trial), and that arm(s) may be stopped.**

Conclusions



- All of these studies will provide evidence to allow a determination of best practice for the ELBW Infant
- The best practice may differ for the infants < 26 weeks compared to infants > 26 weeks
- We should hold any judgments till we evaluate longer –term outcomes to avoid the mistakes of the past!!

Site Concerns

- **We will be using CPAP for infants that we currently intubate and give early surfactant and these are proven interventions and our babies do OK– The CPAP infants are at a significant disadvantage!**

✓ **None of the surfactant studies compared surfactant to CPAP**

✓ **CPAP by itself can improve gas exchange and improve lung volume, avoids intubation, and a number of population and site experiences have demonstrated that its use is associated with lower BPD**

- **I'm not convinced, how will I convince others?**

✓ **We are one of 3 studies comparing early CPAP with surfactant, the others are COIN and the VON trial. We are studying the most immature infants.**

✓ **Without these studies there will never be an answer to this issue and many units are beginning to use more CPAP.**

✓ **The sooner we do this, the sooner we will have an answer**

✓ **The overall incidence of BPD in the Network is not as low as many units report, and BPD is an important predictor of later neurodevelopmental impairmant**

Site Concerns

- **The protocol for the Surfactant infants will result in these infants being kept on the ventilator for longer than they are at present.**

✓ **We currently keep infants on the ventilator for significant durations – Median = 25 (Lowest = 17)days for infants in the small strata and the extubation criteria parallel those used by 2 best practice Network centers**

✓ **It is unclear if infants are currently extubated at these criteria – thus many infants will be intubated at ≥ 15 days when you can use whatever criteria you normally use (The criteria are in place for 14 days only!!)**

Site Concerns

- **We have all become more permissive and the PaCO2 for the Control/Surfactant infants is not high enough**

✓ **The value of 50 torr is only 2 lower than the target for the previous permissive ventilation study.**

✓ **We are trying to keep a separation between the CPAP infants (they require a PaCO2 of 65 torr)**

✓ **Permissive hypercapnia is not yet an evidence based intervention/practice in the ELBW infant**

✓ **We do not think that this single criteria will inhibit extubation of many control infants**

Site Concerns

- **What about infants with apnea needing repeated intervention, infants with sepsis or shock?**

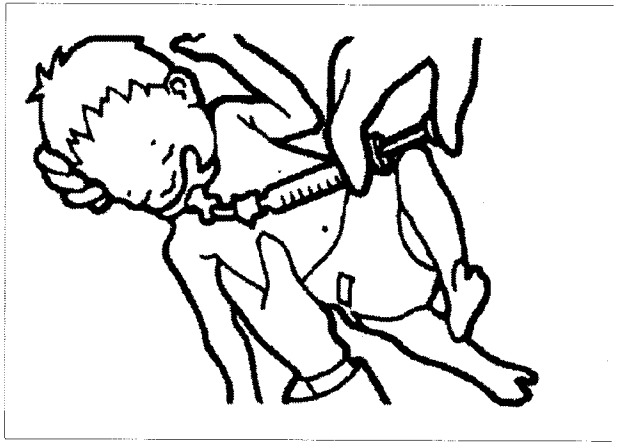
✓ **They may be intubated as needed and this is not considered as a protocol violation.**

- **If an infant self extubates before meeting criteria, do we need to re-intubate?**

✓ **Absolutely NOT!!**

Site Concerns

- **We currently don't give early surfactant and this protocol will be a dramatic change**
- ✓ **There is now substantial evidence that early surfactant before 2 hours is a beneficial intervention and will be a Leapfrog criteria – Your outcomes should improve**



Site Concerns

- **We have some experience with CPAP in the NICU, why do we need to start in the DR?**

✓ **The suggestion from previous studies is that CPAP at birth will help establish lung volume and function, and that it may improve gas exchange as much as surfactant. If the lungs are not allowed to fully expand at birth, it may be more difficult to improve lung function with CPAP started later. In addition, CPAP may prevent some of the inflammation seen with ventilation. One of the benefits of CPAP may be the avoidance of over-ventilation and the associated baro- volu trauma**

Site Concerns

- **From our experience to date we expect a significant number of CPAP infants to fail, especially in the smaller strata – Is this a problem?**

✓ **We agree that many will fail, perhaps 50%. However there is data that suggests that delaying intubation and ventilation may decrease BPD, which is also related to the overall duration of ventilation. The CPAP infants will hopefully spend less time on the ventilator. In addition, CPAP infants should receive surfactant if intubated in the first 48 hours.**

Site Concerns

- **I have reviewed the Oximeter arm and the deviation. I think that we will know whether an infant is on a high or low reading oximeter**
- ✓ **We hope that the blinding will be effective. We have tested the oximeters and don't think that this will be a problem. You are going to be using the same alarm limits that you use currently, and the time that most people look at the oximeter is when it is alarming – at that time the displayed value is the real value.**

Site Concerns

- **If a baby comes off the study oximeter and then goes back on oxygen before 36 weeks, will the baby be on the same kind of oximeter?**

✓ **Yes, the coordinators will have the ability to select the proper type of oximeter.**

Site Concerns

- **Why do the criteria apply for only 14 days?**

✓ **We believe that the major differences in the ventilation arm are the use of early surfactant versus early CPAP. We do not want to artificially separate the treatments to make the groups more different, but rather are trying to compare a non-invasive approach with the traditional one. We want our results to be generally applicable. After initial extubation, the Control/Surfactant infants will be treated following your standard of care.**

Site Concerns

- **In our unit and at Columbia, we wouldn't intubate an infant on CPAP at 50% FiO2 and/or a PaCO2 of 65 torr.**

✓ **Probably so, but no one is certain of the criteria used at Columbia since they depend on individual judgment, not protocol. These criteria are more severe than have been utilized in any trial, and as far as we can tell, are more severe than used in most Network centers. Oh, by the way, you *DON"T HAVE TO INTUBATE THE INFANT AT THESE CRITERIA!! The protocol says MAY INTUBATE!!***

Site Concerns

- **We believe that the best approach may be to intubate, give surfactant and then extubate to CPAP.**
- **You may be right – One arm of VON will test this approach in more mature infants (> 25 weeks). Our study will evaluate the comparability of early CPAP with early surfactant. CPAP infants who fail, will be intubated and receive surfactant, but we expect that this failure will be later than 2 hours. We expect significant numbers of failures in the small strata CPAP infants. We will be monitoring certain outcomes so that we will not do harm if this approach is problematic**

Site Concerns

- **What if one of our approaches leads to worse outcomes?**

✓ **We are going to monitor the occurrence of Grade 3 and 4 IVH, air leaks on admission or in the first 14 days, the need for compressions or epinephrine in the DR and death during the trial. If these occurrences are greater in any arm(s) of the trial, this information will be available to the DSMC (which has been expanded for this trial), and that arm(s) may be stopped.**