AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

691971 ication carefully.

Do not exceed character length restrictions indicated on

* PI: FANAROFF, AVROY
Grant #: 1 U10 HD021364-16
Dual:
IRG: ZHD1 SRC(99)

Council: 01/2001
Received: 06/11/2000

1. TITLE OF PROJECT

Multicenter Network of Neonatal Intensive Care Units

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*

Number: RFA-HD-00-010 Title: Cooperative Multicenter Neonatal Research Network

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — New Investigator ☐ YES

3a. NAME *(Last, first, middle)*	3b. DEGREE(S)	3c. SOCIAL SECURITY NO.
Fanaroff, Avroy A.	MD	SSN

3d. POSITION TITLE	3e. MAILING ADDRESS *(Street, city, state, zip code)*
Professor, Division Co-Director	Rainbow Babies & Children's Hospital
3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT	11100 Euclid Avenue
Pediatrics	Cleveland, OH 44106-6010
3g. MAJOR SUBDIVISION	
School of Medicine	
3h. TELEPHONE AND FAX *(Area code, number and extension)*	
TEL: 216-844-3387	E-MAIL ADDRESS:
FAX: 216-844-3380	aaf2@po.cwru.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date	Full IRB or Expedited Review	4b. Assurance of compliance No.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	5b. Animal welfare assurance no.
☐ No ☒ Yes	8/18/99, 5/16/00, 4/24/00, 5/22/00, 6/16/00	☒ ☐	M1521	☒ No ☐ Yes		A 3145-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year-MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
04/01/01	03/31/06	122,276.	187,082.	644,621.	986,270.

9. APPLICANT ORGANIZATION

Name: Case Western Reserve University
Address: 10900 Euclid Avenue
Cleveland, Ohio 44106-7015

10. TYPE OF ORGANIZATION

Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE: 01

12. ENTITY IDENTIFICATION NUMBER: 34-1018992-A1
DUNS NO. (If available): 07-775-8407

Congressional District: 11

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE

Name: Anne Duli
Title: Director
Address: Research Office
School of Medicine
10900 Euclid Avenue
Cleveland, Ohio 44106-4919

Telephone: (216)-368-4432
FAX: (216) 368-4805
E-Mail: medres@po.cwru.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION

Name: Robin Trail
Title: Assistant Director
Address: Office of Research Admin.
Case Western Reserve Univ.
10900 Euclid Avenue
Cleveland, Ohio 44106-7015

Phone: (216) 368-4510
FAX: (216) 368-4679
E-Mail: resadm@po.cwru.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* Avroy A Fanaroff — DATE: 7/6/00

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)* Robin Trail — DATE: 7/7/00

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This continuation application demonstrates the presence of all the requirements for our Center to remain a key Network member. We have been a productive member of all Network functions including study design, patient recruitment, manuscript preparation, committee membership and leadership. We have demonstrated the ability to collaborate in a collegial manner with other Network centers. We have also been productive beyond the confines of the Network in terms of collaborative studies, bench and clinical research as well as publications. There are 15 Board certified academic neonatologists who ensure protected time for Network activities. Each year we admit more than 1000 babies to the NICU, including approximately 200 with birth weights < 1.5 kg. The adjacent obstetric service delivers almost 5000 babies each year, many high risk, and is supported by four maternal-fetal specialists with interest in clinical research and commitment to the Network concept. Our subspeciality designated (former level III) perinatal center includes modern facilities for labor and delivery, neonatal intensive care and convalescent care. There is a full complement of pediatric medical and surgical subspecialities together with strongly nationally recognized programs in respiratory therapy, nursing, pharmacy, genetics, nutrition, radiology and pediatric pathology. There is a biochemistry, hematology, immunology and microbiology laboratory together with a full service blood bank. The Radiology Department is equipped with standard radiography and the latest generation of ultrasound, CT scanning, MR and PET scanners. Our follow-up program has been nationally acclaimed and boasts in excess of 90% follow-up rate for study patients. The computerized neonatal/perinatal and follow-up data systems have supported a number of studies. We have transmitted our data to the Data Center in a timely and accurate manner. Our experienced nurse coordinator and clinical research nurse team ensure high enrollment rates and compliance with protocols. There is a firm divisional, departmental and institutional commitment to participate in a collaborative manner with other centers. CWRU is proud of its record within the Network and strongly desires to continue to participate. We accept the budgetary process and have submitted an exciting concept protocol for consideration by the Network. In summary, we comfortably satisfy all the criteria for Network participation. We have the personnel, the facilities, the patient base, the data bases and, above all, the experience and commitment. We have firm institutional backing, have demonstrated remarkable productivity and the ability to collaborate, hence fulfill all Network selection criteria.

PERFORMANCE SITE(S) (organization, city, state)
Rainbow Babies & Children's Hospital
11100 Euclid Avenue
Cleveland, OH 44106-6010

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Avroy A. Fanaroff, M.D.	Case Western Reserve University School of Medicine	Principal Investigator
Maureen Hack, M.D.	Case Western Reserve University School of Medicine	Investigator
Michele C. Walsh-Sukys, M.D.	Case Western Reserve University School of Medicine	Investigator

RESEARCH GRANT
TABLE OF CONTENTS

*Type density and type size of entire application must conform to limits provided in instructions on page 6.

Appendix *(Five collated sets. No page numbering necessary for Appendix)*

Number of publications and manuscripts accepted or submitted for publication *(Not to exceed 10)*: _____

Other items (list): [X] Check if Appendix is included

DD

Principal Investigator/Program Director *(Last, first, middle)*: F[redacted]ff, AA

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM	THROUGH
04/01/01	3/31/02

PERSONNEL *(Applicant organization only)*					DOLLAR AMOUNT REQUESTED *(omit cents)*		
NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Fanaroff, AA	Principal Investigator	#	%	$	$14,130	$3,179	$17,309
Newman, N	Research Nurse				$52,809	$11,882	$64,691
Sterl, J	Data Coordinator				$17,613	$3,963	$21,576
							$0
SUBTOTALS →					$84,552	$19,024	$103,576

CONSULTANT COSTS		
EQUIPMENT *(Itemize)*		0.
SUPPLIES *(Itemize by category)*		
Office Supplies	1,500.	
Forms	2,000.	
Communication & Shipping	1,000.	4,500.
TRAVEL		
10 Trips		$11,700
PATIENT CARE COSTS — INPATIENT		$0
PATIENT CARE COSTS — OUTPATIENT		$0
ALTERATIONS AND RENOVATIONS *(Itemize by category)*		
OTHER EXPENSES *(Itemize by category)*		
Photocopy	1,750.	
X-ray	380.	
Printing	250.	
Periodicals	120.	$2,500
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$ $122,276**
CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS		
CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATION COSTS		
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* →		**$ $122,276**

= Months Dedicated to Project
$ = Institutional Based Salary
% = Percentage of Effort

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD

DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD (from Form page 4)	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNE	*Base Salary*	84,552.	86,664.	88,841.	91,082.	93,390.
	Fringe Benefits	19,024.	19,933.	20,807.	21,334.	21,876.
CONSULTANT COSTS		0.	0.	0.	0.	0.
EQUIPMENT		0.	0.	0.	0.	0.
SUPPLIES		4,500.	4,500.	4,500.	4,500.	4,500.
TRAVEL		11,700.	12,051.	12,413.	12,785.	13,169.
PATIENT CARE COSTS	INPATIENT	0.	0.	0.	0.	0.
	OUTPATIENT	0.	0.	0.	0.	0.
ALTERATIONS AND RENOVATIONS		0.	0.	0.	0.	0.
OTHER EXPENSES		2,500.	2,500.	2,500.	2,500.	2,500.
SUBTOTAL DIRECT COSTS		122,276.	125,648.	129,061.	132,201.	135,435.
CONSORTIUM/ CONTRACTUAL COSTS	Direct					
	F&A	0.	0.	0.	0.	0.
TOTAL DIRECT COSTS		122,276.	125,648.	129,061.	132,201.	135,435.

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT *(Item 8a, Face Page)* → $ **644,621.**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Please see attached sheet.

Budget Justification

PERSONNEL:

Dr. Avroy A. Fanaroff is a Professor of Pediatrics at Case Western Reserve University and is Co-Director of the Division of Neonatology at Rainbow Babies & Children's Hospital of University Hospitals of Cleveland. As Principal Investigator, he will devote at least 10% of his time overseeing all aspects of this project. He has devoted the last 30 years to studying all aspects of newborn care.

Nancy Newman, R.N. has been the Nurse Coordinator for the NICU Network project at Rainbow Babies & Children's Hospital for the past 15 years. She has participated in the development of many of the research protocols for the Network, and has been a leader amongst the Network coordinators. She has facilitated all the activities with Institutional Review Board ensuring that our center has consistently been amongst the first prepared to enroll patients in Network trials.

Janet Sterl has performed as Data Coordinator for the project at this institution since 1992. She devotes at least [%] of her time to the collection and entry of data for the Network. She is in frequent communication with the personnel of the Network ensuring that our institution is in full compliance with the needs of the Network.

SUPPLIES:

Three of the items requested, the printer [$450], the RAM for three computers [$1350] and the software for the Office of Neonatology [Paradox & Excel] will be purchased in year 01 of the grant. The $2550 spent on these items in year 01 will be needed in future years for software updates, for computer maintenance agreements, for fax machine maintenance, etc.

The remainder of the funds in this category will be used for toner cartridges for HP Laser Jet III printers as well as for toner for the fax and copy machines, for diskettes, for patient file folders, and the printing of appointment cards, for batteries for pagers and dictaphones. Other supplies needed for the operation of this project are paid for by the Division of Neonatology.

TRAVEL:

Funds have been requested for 10 trips at $1200 each for the Network team [PI & Research Nurse] to travel to Network headquarters.

OTHER EXPENSES:

Funds have been requested for photocopying, shipping and postage expenses, X-rays and scans, and phone/fax expenses.

% = Percentage of Effort

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Avroy A. Fanaroff, M.D.	Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of the Witwatersrand	MB, BCh	1960	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1975 Director, Nurseries, University Hospitals of Cleveland, Cleveland, OH
1981 Professor, Pediatrics, CWRU School of Medicine, University Hospitals of Cleveland, Cleveland, OH
1985 Professor, Reprod Biol, CWRU School of Medicine, University Hospitals of Cleveland, Cleve OH
1992 The Best Doctors in America, 1st ed., Woodward/White
1994 The Best Doctors in America, 2nd ed., Woodward/White
1994 American Academy of Pediatrics Professional Education Award
1996 The Best Doctors in America: Midwest Region, Woodward/White
1999 American Academy of Pediatrics, Perinatal Section's National Neonatology Education Award

PUBLICATIONS

Hack M, Wright LL, Shankaran S, Tyson JE, Horbar JD, Bauer CR, Younes N: Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Network, November 1989-October 1990. Amer J Obstet Gynecol 172:457-464, 1995.

Wright LL, Verter J, Younes N, Stevenson DK, Fanaroff AA, Shankaran S, Ehrenkranz RA, Donovan EF: Antenatal corticosteroid administration and neonatal outcome in very low birthweight infants: The NICHD Neonatal Research Network. Amer J Obstet Gynecol 173:269-274, 1995.

Fanaroff AA, Wright LL, Stevenson DK, Shankaran S, Donovan EF, Ehrenkranz RA, Younes N, Korones SB, Stoll BJ, Tyson JE,Bauer CR, Oh W, Lemons JA, Papile LA: Very low birthweight outcomes of the NICHD Neonatal Research Network, May 1991-December 1992. Am J Obstet Gynecol 173(5):1423-1431, 1995.

Hook B, Hack M, Morrison S, Borawski-Clark E, Newman N, Fanaroff A: Pneumo-pericardium in very low birth weight infants. J Perinatol 15:27-31, 1995.

Stoll BJ, Fanaroff AA: Early-onset coagulase-negative staphylococcal sepsis in the preterm neonate. Lancet 345:1236-1237, 1995.

Fanaroff AA, Baley JE: Use of immunoglobulins for the prevention of serious infections in premature neonates. Neonatal Monitor 11:2-5, 1995.

Stoll BJ, Fanaroff AA: Coagulase-negative staphylococcal sepsis in preterm neonates. Lancet 346:51, 1995.

Stoll BJ, Gordon T, Korones S, Shankaran S, Tyson J, Bauer C, Fanaroff A, Lemons J, Donovan E, Oh W, Stevenson D, Ehrenkranz R, Papile L, Verter J, Wright L: Early-onset sepsis in very low birthweight neonates: A report from the NICHD Neonatal Research Network. J Pediatr 129:72-80, 1996.

Stoll BJ, Gordon T, Korones S, Shankaran S, Tyson J, Bauer C, Fanaroff A, Lemons J, Donovan E, Oh W, Stevenson D, Ehrenkranz R, Papile L, Verter J, Wright L: Late-onset sepsis in very low birthweight neonates: A report from the NICHD Neonatal Resarch Network. J Pediatr 129:63-71, 1996.

Vreman HJ, Verter J, Oh W, Fanaroff AA, Wright LL, Lemons JA, Shankaran S, Tyson JE, Korones SB, Bauer CR, Stoll BJ, Papile LA, Donovan EF, Ehrenkranz RA, Stevenson DK for the NICHD Neonatal Research Network: Interlaboratory variability of bilirubin measurement. Clin Chem 42:869-873, 1996.

Hook B, Kiwi R, Amini SB, Fanaroff A, Hack M: Neonatal morbidity after elective repeat cesarean section and trial of labor. Pediatrics 100:348-353, 1997.

Shankaran S, Papile L-A, Wright LL, Ehrenkranz RA, Mele L, Lemons JA, Korones SB, Stevenson DK, Donovan EF, Stoll BJ, Fanaroff AA, Oh W: The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. N Engl J Med 337:466-471, 1997.

Raghavan CV, Super DM, Chatburn RL, Savin SM, Fanaroff AA, Kalhan SC: Estimation of total body water in very-low-birth-weight infants by using anthropometry with and without bioelectrical impedance and H2[(18)O]. Am J Clin Nutr 68:668-674, 1998.

Wilson-Costello D, Borawski E, Friedman H, Redline R, Fanaroff AA, Hack M: Perinatal correlates of cerebral palsy and other neurologic impairment among very low birthweight children. Pediatrics 162:315-322, 1998.

Fanaroff AA, Korones SB, Wright LL, Verter J, Poland RL, Bauer CR, Tyson JE, Philips JB, III, Edwards W, Lucey JF, Catz CS, Shankaran S, Oh W: The incidence, presenting features, risk factors, and significance of late-onset septicemia in very low-birth-weight infants. Pediatr Infect Dis J 17:593-598, 1998.

Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, Papile LA, Bauer CR, Stoll BJ, Tyson JE, Shankaran S, Fanaroff A, Donovan E, Ehrenkranz R, Verter J: Very-low-birth-weight [VLBW] outcomes of the NICHD Neonatal Research Network, January 1993 through December 1994. Am J Obstet Gynecol 179:1632-1639, 1998.

Donovan EF, Ehrenkranz RA, Shankaran S, Stevenson DK, Wright LL, Younes J, Fanaroff AA, Korones SB, Stoll BJ, Tyson JE, Bauer CR, Lemons JA, Oh W, Papile L-A: Outcomes of very-low-birth-weight twins cared for in the NICHD Neonatal Research Network's intensive care units. Am J Obstet Gynecol 197:742-749, 1998.

Papile LA, Tyson JE, Stoll BJ, Wright LL, Donovan EF, Bauer CR, Krause-Steinrauf H, Verter J, Korones SB, Lemons JA, Fanaroff AA, Stevenson DK, Oh W, Ehrenkranz RA, Shankaran S: Multicenter trial of two dexamethasone therapy regimens in ventilator-dependent premature infants. N Engl J Med 338:1112-1118, 1998.

Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M: Placental lesions associated with neurologic impairment and cerebral palsy in very low-birth-weight infants. Arch Pathol Lab Med 122:1091-1098, 1998.

Cairo MS, Agosti J, Ellis R, Laver JJ, Puppala B, deLemos R, Givner L, Nesin M, Wheeler G, Seth T, van de Ven C, Fanaroff AA: A randomized, double-blind, placebo-controlled trial of prophylactic recombinant human granulocyte-macrophage colony-stimulating factor to reduce nosocomial infections in very low birth weight neonates. J Pediatr 134:64-70, 1999.

Hack M, Fanaroff AA: Outcomes of children of extremely low birthweight and gestational age in the 1990s. Early Hum Dev 53:193-218, 1999.

Donovan EF, Tyson JE, Ehrenkranz RA, Verter J, Wright LL, Korones SB, Bauer CR, Shankaran S, Stoll BJ, Fanaroff AA, Oh W, Lemons JA, Stevenson DK, Papile LA: Inaccuracy of Ballard scores before 28 weeks' gestation. National Institute of Child Health & Human Development Neonatal Research Network. J Pediatr 135:147-152, 1999.

Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, Katsikiotis V, Tyson JE, Oh W, Shankaran S, Bauer CR, Korones SB, Stoll BJ, Stevenson DK, Papile LA: Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 104:280-289, 1999.

Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR, Korones SB, Fanaroff AA: Vitamin A supplementation for extremely- low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 340:1962-1968, 1999.

Stoll BJ, Temprosa M, Tyson JE, Papile LA, Wright LL, Bauer CR, Donovan EF, Korones SB, Lemons JA, Fanaroff AA, Stevenson DK, Oh W, Ehrenkranz RA, Shankaran S, Verter J: Dexamethasone therapy increases infection in very low birth weight infants. Pediatrics 104:e63, 1999.

Fanaroff AA: Challenges for neonatology and neonatologists. J Perinatol 19:329, 1999.

Fanaroff AA, Hack M: Periventricular leukomalacia - prospects for prevention. N Engl J Med 341:1229-1231, 1999.

Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, Verter J, Stoll BJ, Lemons JA, Papile LA, Shankaran S, Donovan EF, Oh W, Ehrenkranz RA, Fanaroff AA: Persistent pulmonary hypertension of the newborn in the era before nitric oxide: Practice variation and outcomes. Pediatrics 105:14-20, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Maureen Hack, M.B., Ch.B.	Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Pretoria Univ Med School, South Africa	M.B., Ch.B.	1959	Medicine
Pediatric Residency, Sheba Med Ctr, Israel		1961-65	Pediatrics
Heart Institute, Sheba Med Ctr, Israel	Fellowship	1970	Pediatric Cardiology
Case Western Res Univ, Cleveland, OH	Fellowship	1973-75	Neonatology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. ***DO NOT EXCEED TWO PAGES.***

PROFESSIONAL APPOINTMENTS

1966-1968 Associate, Dept. Neonatology, Sheba Medical Center, Israel
1970-1976 Associate Director, Dept. Neonatology, Newborn & Premature Nurseries, Sheba Medical Center, Israel
1977-1982 Assistant Professor, Dept. Pediatrics, Case Western Reserve University, Cleveland, Ohio
1977-present Director, High Risk Follow-up Program
1982-1991 Associate Professor, Dept. Pediatrics
1991-present Professor, Pediatrics; Professor, Reproductive Biology

SELECTED PUBLICATIONS

Hack M, Brish M, Serr DM, Insler V, Lunenfeld B: Outcome of pregnancy after induced ovulation: Follow-up of pregnancies and children born after gonadotropin therapy. JAMA 211:791-797, 1970.

Hack M, Brish M, Serr DM, Insler V, Lunenfeld B: Outcome of pregnancy after induced ovulation: Follow-up of pregnancies and children born after clomiphene therapy. JAMA 220:1329-1333, 1972.

Hack M, Mostow A, Miranda S: Development of attention in preterm infants. Pediatrics 58:669-674, 1976.

Hack M, Fanaroff AA, Merkatz IR: The low birth weight infant. Evolution of a changing outlook. N Engl J Med 301 (21):1152-1165, 1979.

Hack M, Merkatz IR, Jones P, Fanaroff AA: Changing trends of neonatal and postneonatal deaths in very low birthweight infants. Am J Obstet Gynecol 137: 797-800, 1980.

Hack M, Demonterice D, Merkatz IR, Jones P, Fanaroff AA: Rehospitalization of the very low birthweight infant a continuum of perinatal and environmental morbidity. Am J Dis Child 135:263-266, 1981.

Hack M, Gordon D, Merkatz IR, Jones PK, Fanaroff AA: The prognostic significance of postnatal growth in very low birthweight infants. Am J Obstet Gynecol 143: 693-699, 1982.

Hack M, Rivers A, Fanaroff AA: The very low birthweight infant: The broader spectrum of morbidity during infancy and early childhood. J Dev Behav Pediatr 4:343-349, 1983.

Hack M, Merkatz IR, McGrath SK, Jones PK, Fanaroff AA: Catch-up growth in very low birthweight infants: potential and clinical correlates. Am J Dis Child 138:1370- 1375, 1984.

Klein N, Hack M, Gallagher J, Fanaroff AA: School performance of the normal intelligence very low birthweight infant. Pediatrics 75:531-537, 1985.

Hack M, Breslau N: Effects of brain growth in infancy on 3 year IQ in very low birth-weight infants. Pediatrics 77:196-202,1986.

Hack M, Fanaroff A: Delivery room care of the fetal infant: effects on morbidity and outcome. N Engl J Med 314:660-664, 1986.

Rivers A, Hack M: Experience of families with very low birthweight children with neurologic sequelae. Clin Pediatr 26:223-230, 1987.

Klein NK, Hack M, Breslau N, Fanaroff A: Children who were very low birthweight: development and academic

achievement at nine years of age. Dev Behav Pediatr 10:32-37, 1989.
Hack M, Breslau N, Rivers A, Fanaroff AA: The appropriate and small for gestational age very low birthweight infant: differential effects of brain growth failure on outcome. Am J Dis Child 143:63-68, 1989.
Hack M, Fanaroff AA: Outcome of extremely low birthweight infants 1982-1988. N Engl J Med 321:1642-1647, 1989.
Skidmore MD, Rivers A, Hack M: Increased risk of cerebral palsy among very low birth weight infants with chronic lung disease. Dev Med Child Neurol 32:325-332, 1990.
Hack M, Horbar JD, Malloy MH, Tyson JE, Wright L, Wright E: Very low birthweight outcomes of the NICHD neonatal network. Pediatrics 87:587-597, 1991.
Aram DM, Hack M, Hawkins S, Weissman BM, Borawski E: Very low birthweight children and speech and language development. J Speech Hear 34:1169-1179, 1991.
Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E: Effects of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 325:231-237, 1991.
Hack M, Breslau N, Aram D, Weissman B, Klein N, Borawski-Clark E: The effect of very low birth weight and social risk on neurocognitive abilities at school age. J Dev Behav Pediatr, 13:412-420, 1992.
Hack M, Weissman B, Breslau N, Klein N, Borawski-Clark E, Fanaroff A: Health of very low birthweight children during their first 8 years. J Pediatr 122:887-892, 1993.
Hack M, Fanaroff AA: Outcomes of extremely immature infants - a perinatal dilemma (editorial). N Engl J Med 329:1649-650, 1993.
Hack M, Taylor G, Klein N, Eiben R, Schatschneider C, Mercuri Minich N: School age outcome of a regional cohort of <750 gm birthweight children. N Engl J Med 331:753-659, 1994.
Taylor HG, Klein N, Hack M (1995). Academic functioning in <750 gm birthweight children who have normal cognitive abilities: evidence for specific learning disabilities. J Pediatr Psychol, 20:703-719.
Furman L, Hack M, Watts C, Borawski-Clark E, Baley J, Amini S, Hook B: Twenty-month outcome of ventilator dependent very low birthweight children born during the early years of dexamethasone therapy. J Pediatr 126:434-440, 1995.
Hack M, Wright LL, Shankaran S, Tyson JE, Horbar JD, Bauer CR, Younes N, Malloy M: Very low birthweight outcomes of the NICHD Neonatal Network November 1989 - October 1990. Am J Obstet Gynecol 172:457-464, 1995.
Hack M, Merkatz IR: Preterm delivery and low birth weight - a dire legacy. N Engl J Med 333:1772-1774, 1995.
Hack M, Weissman B, Borawski-Clark E: Catch-up growth can occur during childhood in VLBW (<1.5 kgm birthweight) children. Arch Pediatr Adolesc Med 150:1122-1129, 1996.
Wilson D, Rao P, Morrison S, Hack M: Radiation dose from x-rays to <750 gm birthweight survivors. Pediatrics 97:369-375, 1996.
Hack M, Friedman H, Fanaroff AA: Outcome of <750 gm birthweight survivors in the era of surfactant. Pediatrics 98:931-937, 1996.
Furman L, Baley J, Borawski-Clark E, Hack M: The spectrum of hospitalizations among very low birthweight infants with chronic lung disease. J Pediatr 128:447-452, 1996.
Taylor HG, Klein N, Schatschneider C, Hack M: Predictors of early school age outcomes in very low birthweight children. J Dev Behav Pediatr 19:235-243 1998, 1998.
Furman L, Minich NM, Hack M: Breastfeeding of very low birthweight infants. J Human Lactation 14(1) 29-34, 1998.
Wilson-Costello D, Borawski E, Friedman H, Redline R, Fanaroff AA, Hack M: Perinatal correlates of cerebral palsy and other neurologic impairment among very low birthweight children. Pediatrics 162:315-322, 1998.
Hack M, Fanaroff AA: Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Human Dev 53: 193-218, 1999.
Hack M: Consideration of the use of health status, functional abilities and quality of life to monitor neonatal intensive care practice. Pediatrics On Line Supplement. Pediatrics 103: 312-328, 1999.

Pending Publication

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Michele C. Walsh-Sukys, M.D.	Associate Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Univ of California at Davis	B.S.	1978	Human Development
Case Western Reserve University	M.D.	1982	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL APPOINTMENTS

1982-1985	Pediatric Resident, University Hospitals of Cleveland, Cleve., OH
1985-1987	Neonatal/Perinatal Medicine Fellow, University Hospitals of Cleveland, Cleve., OH
1988-1989	Sr Instructor, Pediatrics, Department of Pediatrics, Case West Res Univ, Cleve., OH
1989-1995	Assistant Professor, Pediatrics, Case Western Reserve University, Cleve., OH
1991-present	Medical Director, NICU, Rainbow Babies & Childrens Hospital, Cleve., OH
1993-1997	Vice Chairman for Patient Care, Rainbow Babies & Childrens Hospital, Cleve., OH
1995-present	Associate Professor, Pediatrics, Case Western Reserve University, Cleve., OH

AWARDS/HONORS

1979	National Foundation March of Dimes Research Award
1981	Alpha Omega Alpha Honor Society, Case Western Reserve University
1982	Alice Paige Cleveland Prize for Leadership
1982	Departmental Award for Excellence in Pediatrics
1986-1987	National Research Service Award
1990	Teaching Excellence Award, Department of Pediatrics

PUBLICATIONS - MANUSCRIPTS; PEER REVIEWED

Walsh MC, Carlo WA: Sustained inflation during high frequency oscillatory ventilation improves pulmonary mechanics and oxygenation. J Appl Physiol 65:368-372, 1988.

Walsh MC, Carlo WA: Determinants of gas flow through a bronchopleural fistula (BPF). J Appl Physiol 67:1591-1596, 1989.

Carlo WA, Beoglos A, Chatburn RL, **Walsh MC**, Martin RJ: High-frequency jet ventilation in neonatal pulmonary hypertension. Am J Dis Child 143:233-238, 1989.

Spector ML, Wiznitzer M, **Walsh-Sukys MC**, Stork EK: Carotid reconstruction in the neonate following ECMO. J Pediatr Surg 26:357-361, 1991.

Wiznitzer M, Masaryk TJ, Lewin JS, Stork EK, **Walsh-Sukys MC**: Parenchymal and vasculature magnetic resonance imaging after ECMO. Am J Dis Child 144:1323-1326, 1991.

Walsh-Sukys MC, Cornell DJ, Stork EK: The natural history of direct hyperbilirubinemia associated with ECMO. Am J Dis Child 146:1176-1180, 1992.

Walsh-Sukys MC, Cornell DJ, Houston LN, Keszler M, Kanto W Jr: Treatment of persistent pulmonary hypertension of the newborn without hyperventilation: Assessment of the diffusion of an innovation. Pediatrics 94:303-306, 1994.

Walsh-Sukys MC, Bauer R, Cornell DJ, Friedman H, Stork EK, Hack M: Severe respiratory failure in neonates: Mortality, morbidity and neurodevelopmental outcome. J Pediatr 125:104-110, 1994.

Pending Publication

Kinsella JP, Walsh WF, Bose CL, Gerstmann DR, Labella JJ, Sardesai S, **Walsh-Sukys MC**, et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. Lancet 1999; 354:1061-1065.

Martin RJ, **Walsh-Sukys MC**. Bronchopulmonary dysplasia--no simple solution. N Engl J Med 1999; 340:1036-1038, 1999.

Walsh-Sukys MC, Tyson JE, Wright LL et al: Persistent pulmonary hypertension of the newborn in the era before nitric oxide: Practice variation and outcomes. Pediatrics 2000; 105:14-20.

Pending Publication

MONOGRAPHS

Walsh-Sukys MC, Kliegman RM (eds.): Perinatal Clinics of North America: Controversies in Perinatology II. W.B. Saunders, Philadelphia, 1993.

Walsh-Sukys MC, Krug S: Procedures in Infants and Children. WB Saunders, Philadelphia, 1997.

ABSTRACTS

Walsh MC, Falahat AR, Carlo WA: Effect of negative thoracostomy pressure on bronchopleural fistula (BPF) flow. Pediatr Res 23:1366, 1988.

Walsh MC, Falahat AR, Carlo WA: Mean airway pressure determines bronchopleural fistula (BPF) flow during assisted ventilation. Pediatr Res 23:429A, 1988.

Carlo WA, Beoglos A, **Walsh MC**, Chatburn RL, Stork EK, Martin RJ: Can high-frequency jet ventilation (HFJV) avert the need for extracorporeal membrane oxygenation (ECMO)? Pediatr Res 23:1211, 1988.

Walsh MC, Falahat AR, Carlo WA: Influence of high frequency ventilation on bronchopleural fistula flow and gas exchange. Am Rev Resp Dis 139:A438, 1989.

Walsh MC, Cornell DJ, Slater-Myer L et al: Direct hyperbilirubinemia (DB) associated with extracorporeal membrane oxygenation (ECMO). Pediatr Res 25:235A, 1989.

Litmanovitz I, Marx C, Ksenich RA, Cornell DJ, **Walsh-Sukys, MC**: Anticonvulsant therapy on ECMO: In vitro analysis of drug-circuit interactions. Pediatr Res 29:222A, 1991.

Spector ML, Wiznitzer M, Stork EK, **Walsh-Sukys MC**: Common carotid artery (CCA) reconstruction after neonatal extracorporeal membrane oxygenation (ECMO): Discharge and eighteen month follow-up. Pediatr Res 29:235A, 1991.

Walsh-Sukys MC, Leonard ML, Rich EA: Surfactant induced inhibition of GM-CSF stimulated monocyte DNA synthesis. Pediatr Res 29:334A, 1991.

Walsh-Sukys M, Bauer R, Friedman H, Gresky J, Ksenich R, Houston L, Hack M: Survival and 20 month outcome of severe respiratory insufficiency in infants 2.0 kg birthweight. Pediatr Res 31:263A, 1992.

Walsh-Sukys M, Cornell D, Kanto W Jr: Treatment of meconium aspiration syndrome (MAS) and persistent pulmonary hypertension (PPHN) in 1991: A national survey. Pediatr Res 31:228A, 1992.

Walsh-Sukys M, Fanaroff A, Wright L, Verter J, Bauer C, Korones S, Stevenson D, Tyson J: Persistent pulmonary hypertension of the newborn (PPHN): Prospective, multi-center study of treatments and outcomes. Pediatr Res 37:244A, 1995.

Walsh-Sukys M, Fanaroff A, Wright L, Verter J, Bauer C, Korones S, Stevenson D, Tyson J: Persistent pulmonary hypertension of the newborn (PPHN): Practice variation among academic NICUs. Pediatr Res 37:244A, 1995.

Walsh-Sukys M, Tyson J, Fanaroff A, Wright L, Verter J, Bauer C, Korones S, Stevenson D: Use of unproven therapies in critically ill neonates. Pediatr Res 37:40A, 1995.

Walsh-Sukys M, DePompei P, Morney VL et al. Outcomes of a carepath for respiratory distress syndrome. Pediatr Res 43:202A, 1998.

Hoyen C, Rice L, Conte S, **Walsh-Sukys M**, Toltzis P. The use of real time pulse field gel electrophoresis (PFGE) to guide interventions during a nursery outbreak of *Serratia marcesens*. Pediatr Res 43:247A, 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Eileen K. Stork, M.D.	Associate Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Maryland at College Park	BS	1973	Biology
Univ of Maryland Sch Medicine at Baltimore	MD	1978	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1984-1992 Assistant Professor, Pediatrics, Case Western Reserve Univ, Cleveland, OH
1987-present Director, ECMO Center, Rainbow Babies & Children's Hospital, Cleveland, OH
1992-present Associate Professor, Pediatrics, Case Western Reserve Univ, Cleveland, OH
1999-present Clinical Director, Division of Neonatology

HONORS & AWARDS:

Alpha Omega Alpha, National Medical Honor Society
Magna cum laude, University of Maryland School of Medicine
Phi Beta Kappa, University of Maryland at College Park
Alpha Lambda Delta, National Microbiology Honor Society

PUBLICATIONS

Pitha J, Stork EK, Wimmer E: Protein synthesis during aging of human cells in culture Direction by polio virus. Exp Cell Res 94:310-314, 1975.

Stork EK, Wisseman CL, Jr: Growth of rickettsia prowazeki in enucleated cells. Infection and Immunity 13:1743-1748, 1976.

Rome ES, Stork EK, Carlo WA, Martin RJ: Limitations of transcutaneous PO_2 and PCO_2 monitoring in infants with bronchopulmonary dysplasia. Pediatrics 74:217-220, 1984.

Baley JE, Stork EK, Warkentin PI, Shurin SB: Buffy coat transfusions in neutropenic neonates with presumed sepsis: A prospective, randomized trial. Pediatrics 80:712-720, 1987.

Baley JE, Stork EK, Warkentin PI, Shurin SB: Neonatal neutropenia: Clinical manifestations, etiology and outcome. Am J Dis Child 142:1161-1166, 1988.

Baley JE, Bruce M, Stork EK, Klinger J, Medvik K: Granulocyte transfusions in septic adult and newborn rats: Distribution of granulocytes and effect on peripheral blood and bone marrow. J Lab Clin Med 115:283-291, 1990.

Baley JE, Stork EK, Warkentin PI and Shurin SB: Granulocyte transfusion [letter]. Pediatrics 81:915, 1988.

Lewin JS, Masaryk TJ, Modic MT, Ross JS, Stork EK, Wiznitzer M: Extracorporeal membrane oxygenation in infants: Angiographic and parenchymal evaluation of the brain with MR imaging. Radiology 173:361-365, 1989.

Morrison SC, Stork E: Documentation of spontaneous reduction of childhood intussusception by ultrasound. Pediatr Radiol 20:358-359, 1990.

Spector ML, Wiznitzer M, Walsh-Sukys MC, Stork EK: Carotid reconstruction in the neonate following ECMO. J Pediatr Surg 26:357-361, 1991.

Wiznitzer M, Masaryk TJ, Lewin JS, Stork EK, Walsh-Sukys MC: Parenchymal and vasculature magnetic resonance imaging after ECMO. Am J Dis Child, February, 1991.

Walsh-Sukys MC, Cornell DJ, Stork EK: The natural history of direct hyperbilirubinemia associated with ECMO. Am J Dis Child 146:1176-1180, 1992.

Walsh-Sukys M, Stork EK, Martin RJ: Neonatal ECMO: Iron lung of the 1990s? J Pediatr 124:427-430, 1994.

Potter CF, Dreshaj IA, Haxhiu MA, Stork EK, Chatburn RL, Martin RJ: Effect of exogenous and endogenous nitric oxide (NO) on the airway and tissue components of lung resistance in the newborn piglet. Pediatr Res, 41:886-891, 1997.

Lotze A, Mitchell BR, Bulas DI, Zola EM, Shaowitz RA, Gunkel JH: Multicenter study of surfactant [beractant] use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. J Pediatr 132:40-47, 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Deanne E. Wilson-Costello, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Grove City College, Grove City, PA	B.S.	1985	Biology
Wright State Univ Sch of Med, Dayton, OH	M.D.	1991	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1994-1996 Clinical Neonatologist, Marymount Hospital, Cleveland, OH
1994-1995 Clinical Neonatologist, Meridia-Hillcrest Hospital, Cleveland, OH
1994-present General Pediatrics Associate, Dr. Shelly Senders, Cleveland, OH
1995-present Clinical Neonatologist, Bedford Hospital, Bedford, OH
1996-present Clinical Neonatologist, Lake East Hospital, Painesville, OH
1997-present Assistant Professor, Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1998-present Clinical Neonatologist/Co-Director, Geauga Regional Hospital, Chardon, OH

HONORS & AWARDS

1984-1985 Beta Beta Beta National Biology Honor Society
1985 Magna Cum Laude
1987-1988 AHEC Scholarship for Primary Care
1993 American Lung Associate Award
1992-1994 Neonatology Clinical Excellence Award
1994 Pediatric Nurses Award
1994 Zeithaml Senior Resident of the Year
1999, 2000 Pearl Day Teaching Award
1999 Teaching Excellence Award

PUBLICATIONS

Wilson D: Group B strep. Perinatal Perspectives, Spring 1995:9

Wilson-Costello D, Rao P, Morrison S, Hack M: Radiation exposure from diagnostic radiographs in extremely low birthweight infants. Pediatrics 97:369-374, 1996.

Wilson-Costello D, Rao P, Morrison S, Hack M: Radiation exposure of very low birthweight [< 1500 g] infants. Reply letter to editor. Pediatrics 99:142, 1997.

Wilson-Costello D, Borawski E, Friedman H, Redline R, Fanaroff A, Hack M: Perinatal correlates of neurologic impairment among very low birthweight children. Pediatrics 102:315-322, 1998.

Redline RW, Wilson-Costello D, Borawski E, Fanaroff A, Hack M: Placental lesions associated with neurologic impairment and cerebral palsy in very low birth weight infants. Arch Pathol Lab Med 122:1091-1098, 1998.

diastolic function in normal neonates. J Am Coll Cardiol 13:700-705, 1989.

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Martha J. Miller, Ph.D., M.D.	Associate Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Ohio State University, Columbus, OH	B.S.	1962-1965	Organic chemistry
New York Univ. School of Medicine	Ph.D.	1965-1969	Molecular biology
Univ. of Sherbrooke Sch. of Med., Quebec, Canada		1970-1973	Fellow, Biochemistry
Univ. of South. Calif., Los Angeles, CA	M.D.	1973-1977	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1976-1980	Pediatric Residency, University of California Hospital and Clinics, Los Angeles California
1979-1982	Pediatric Cardiology Fellowship, University of California Hospital and Clinics, Los Angeles California
1982-1984	Neonatology Fellowship, Rainbow Babies & Children's Hospital, CWRU, Cleveland, OH
1984-1992	Assistant Professor, Department of Pediatrics, CWRU School of Medicine, Cleveland, OH
1984-present	Clinical staff, Marymount Hospital, Mt. Sinai Medical Center, Meridia-Hillcrest Hospital, Cleveland, OH
1991-present	Director, University MacDonald Women's Hospital nurseries
1993-present	Associate Professor with tenure, Dept Pediatrics, CWRU School of Medicine, Cleveland, OH
1996-present	Clinical staff: Bedford Community Hospital and Lake County Hospital System
1993-1997	Member NIH-HED 1 Study Section

PUBLICATIONS

Miller MJ, Martin RJ, Carlo WA: Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. J Pediatr 106:91-94, 1985.

Miller MJ, Martin RJ, Carlo WA, Fouke JM, Strohl KP, and Fanaroff AA: Oral breathing in newborn infants. J Pediatr 48:947, 1985.

Miller MJ, Carlo WA, Strohl KP, Fanaroff AA, Martin RJ: The effects of maturation on oral breathing in premature infants. J Pediatr 109:515-519, 1986.

Martin RJ, Miller MJ, Carlo WA: Pathogenesis of apnea in preterm infants. J Pediatr 109:733-741, 1986.

Noble LM, Carlo WA, Miller MJ, DiFiore JM, Martin RJ: Transient changes in expiratory time during hypercapnia in premature infants. J Appl Physiol 62:1010-1013, 1987.

Rome ES, Miller MJ, Goldthwait DA, Osorio IO, Fanaroff AA, Martin RJ: Effect of sleep state on chest wall movements and gas exchange in infants with resolving BPD. Pediatr Pulmonol 3:259-263, 1987.

Gauda EB, Miller MJ, Carlo WA, DiFiore JM, Johnsen DC, Martin RJ: Genioglossus response to airway occlusion in apneic versus non-apneic infants. Pediatr Res 22:683-687, 1987.

Martin RJ, Siner BS, Carlo WA, Miller MJ: Effect of head position on distribution of nasal airflow in preterm infants. J Pediatr 112:99-103, 1988.

Martin RJ, Beoglos A, Miller MJ, DiFiore JM, Robertson SR, Carlo WA: The influence of increasing arterial PCO_2 on transcutaneous PCO_2 measurements. Pediatrics 81:684-687, 1988.

Miller MJ, Carlo WA, DiFiore JM, Martin RJ: Airway obstruction during periodic breathing in premature infants. J Appl Physiol 64:2496-2500, 1988.

Martin RJ, Miller MJ, Siner B, DiFiore JM, Carlo WA: Effects of unilateral nasal occlusion on ventilation and pulmonary resistance in preterm infants. J Appl Physiol 66: 2522-2526, 1989.

Gauda EB, Miller MJ, Carlo WA, DiFiore JM, Martin RJ: Genioglossus and diaphragm activity during obstructive apnea

and airway occlusion in infants. Pediatr Res 26:583-587, 1989.
Miller MJ, DiFiore JM, Strohl KP, Martin RJ: The effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. J Appl Physiol 68:141-146, 1990.
Miller MJ, DiFiore JM, Strohl KP, Carlo WA, Martin RJ: The effects of CO_2 rebreathing on pulmonary mechanics in premature infants. J Appl Physiol 70:2582-2586, 1991.
Poskurica-Haxhiu B, Carlo WA, Miller MJ, DiFiore JM, Haxhiu MA, Martin RJ: Maturation of respiratory reflex responses in the piglet. J Appl Physiol 70:608-616, 1991.
Timms BJ, DiFiore JM, Martin RJ, Miller MJ: Alae nasi activation in preterm infants during oral feeding. Pediatr Res 32:679-682, 1992.
Haxhiu-Poskurica B, Haxhiu MA, Kumar GK, Miller MJ, Martin RJ: Tracheal smooth muscle responses to substance P and neurokinin A, and its modulation by neutral endopeptidase in the maturing piglet. J Appl Physiol 72:1090-1095, 1992.
Timms BJM, DiFiore JM, Martin RJ, Miller MJ: Increased respiratory drive as a modulator of oral feeding in premature infants. J Pediatr 123:127-131, 1993.
Miller MJ, DiFiore JM, Petrie TG: Changes in respiratory mechanics and ventilatory timing which accompany apnea in premature infants. J Appl Physiol 75:720-723, 1993.
Haxhiu-Poskurica B, Ernsberger P, Haxhiu MA, Miller MJ, Cattarossi L, Martin R: Development of cholinergic innervation and muscarinic receptor subtypes in piglet trachea. Am J Physiol (Lung Cell Mol Physiol) 264:L606-L614, 1993.
Rodriguez RJ, Dreshaj IA, Kumar G, Miller MJ, Martin RJ: Maturation of the cholinergic response of tracheal smooth muscle in the piglet. Pediatr Pulmonol 18:28-33, 1994.
Dreshaj IA, Martin RJ, Miller MJ, Haxhiu MA: Responses of lung parenchyma and airways to tachykinin peptides in piglets. J Appl Physiol 77:147-151, 1994.
Litmanovitz I, Dreshaj I, Miller MJ, Haxhiu MA, Martin RJ: Central chemosensitivity affects respiratory muscle responses to laryngeal stimulation in the piglet. J Appl Physiol 76:403-408, 1994.
Martin RJ, Dreshaj I, Miller M, Haxhiu MA: Hypoglossal and phrenic responses to central respiratory inhibition in piglets. Respir Physiol 97:93-103, 1994.
Miller MJ, DiFiore JM: A comparison of swallowing during apnea and periodic breathing in premature infants. Pediatr Res 37:796-799, 1995.
Martin RJ, Dreshaj IA, Miller MJ, Haxhiu MA: Neurochemical control of tissue resistance in piglets. J Appl Physiol 79:812-817, 1995.
Martin RJ, DiFiore JM, Korenke CB, Randal H, Miller MJ, Brooks LJ: Vulnerability of respiratory control in healthy preterm infants placed supine. J Pediatr 127:609-614, 1995.
Dreshaj IA, Miller MJ, Ernsberger P, Haxhiu-Poskurica B, Martin RJ, Haxhiu MA: Central effects of endothelin on respiratory output during development. J Appl Physiol 79:420-427, 1995.
van Lunteren E, Vafaie H, Miller MJ: Effects of theophylline on pharyngeal dilator and diaphragm muscle contractile properties. Respiration 63:88-93, 1996.
Miller MJ, Martin RJ: Pathophysiology of apnea of prematurity. IN Polin RA, Fox WW (eds): *Fetal and Neonatal Physiology*, 2nd edition, WB Saunders: Orlando, FL, 1996.
Dimaguila MAVT, DiFiore JM, Martin RJ, Miller MJ: Characteristics of hypoxemic episodes in intubated very low birthweight infants. J Pediatr. 130: 577-583, 1997.
Chelala JL, Kilani S, Miller MJ, Martin RJ, Ernsberger P: Muscarinic receptor binding sites of the M4 subtype in porcine lung parenchyma. Pharmacology and Toxicology 83:200-207, 1998.
Miller MJ, Yike I, Dreshaj G, Dearborn DG, Haxhiu MA: Exposure to *Stachybotrys chartum* causes apnea and alteration in respiratory function in rat pups. Am J Respir Crit Care Med 159: A:431, 1999.

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Richard J. Martin, M.D.	Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Sydney School of Medicine	MBBS	1970	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1970-1972 Junior & Senior Resident Medical Officer, Royal North Shore Hospital of Sydney
1972-1974 Pediatric Resident & Chief Resident, University MO Medical Center, Columbia, MO
1974-1976 Neonatal Fellow, Department of Pediatrics, CWRU School Medicine, Cleveland, OH
1976-1977 Senior Instructor, Case Western Reserve University School of Medicine, Cleveland, OH
1977-1983 Assistant Professor, Pediatrics, CWRU School of Medicine, Cleveland, OH.
1983-1990 Associate Professor, Pediatrics, CWRU School of Medicine, Cleveland, OH
1984-1990 Associate Professor, OB/GYN, Reprod Biol, CWRU School of Medicine, Cleveland, OH
1985-present Co-Director, Neonatology Division, Pediatrics, CWRU School of Medicine, Cleveland, OH
1986-present Award of Tenure, Case Western Reserve University School of Medicine, Cleveland, OH
1990 Professor, Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1990 Professor, Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, OH
1998-present Director, Division of Neonatology, Rainbow Babies & Childrens Hospital, Cleveland, OH
1999 Professor, Physiology, CWRU School of Medicine, Cleveland, OH

SERVICE

1982 Co-Editor, *Neonatal/Perinatal Medicine*, CV Mosby, St. Louis, MO
1999-2003 Permanent Member, Human Embryology and Development Study Section [1], Center for Scientific Review, National Institutes of Health
1999 Member, Journal of Applied Physiology Editorial Board

PUBLICATIONS [Extracted from 102 publications, 43 chapters]

Martin RJ, Miller MJ, Carlo WA: Pathogenesis of apnea in preterm infants. J Pediatr 109:733, 1986.

Miller MJ, Carlo WA, Strohl KP, Fanaroff AA, Martin RJ: The effect of maturation on oral breathing in premature infants. J Pediatr 109:515, 1986.

Miller MJ, Martin RJ, Carlo WA, Fanaroff AA: Oral breathing in response to nasal trauma in term infants. J Pediatr 111:899, 1987.

Gauda EB, Miller MJ, Carlo WA, DiFiore JM, Johnsen DC, Martin RJ: Genioglossus response to airway occlusion in apneic versus nonapneic infants. Pediatr Res 22:683, 1987.

Carlo WA, Chatburn RL, Martin RJ: Randomized trial of high-frequency jet ventilation versus conventional ventilation in respiratory distress syndrome. J Pediatr 110:275, 1987.

Noble LM, Carlo WA, Miller MJ, DiFiore JM, Martin RJ: Transient changes in expiratory time during hypercapnea in premature infants. J Appl Physiol 62:1010-1013, 1987.

Miller MJ, Carlo WA, DiFiore J, Martin RJ: Airway obstruction during periodic breathing in premature infants. J Appl Physiol 64:2496, 1988.

Carlo WA, Martin RJ, DiFiore JM: D[redacted]ences in CO_2 threshold of respiratory mu[redacted] in preterm infants. J Appl Physiol 65:2434, 1988.

HIFI Study Group: High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 320:88-93, 1989.

Gauda EB, Miller MJ, Carlo WA, DiFiore JM, Martin RJ: Genioglossus and diaphragm activity during obstructive apnea and airway occlusion in infants. Pediatr Res 26:583-587, 1989.

Miller MJ, DiFiore JM, Strohl KP, Martin RJ: The effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. J Appl Physiol 68:141-146, 1990.

Haxhiu MA, Haxhiu-Poskurica B, Moracic V, Carlo WA, Martin RJ: Reflex and chemical responses of tracheal submucosal glands in piglets. Respir Physiol 82:267-278, 1990.

Haxhiu-Poskurica B, Carlo WA, Miller MJ, DiFiore JM, Haxhiu MA, Martin RJ: Maturation of respiratory reflex responses in the piglet. J Appl Physiol, 70:608-616, 1991.

Litmanovitz I, Martin RJ, Haxhiu MA, Cattarossi L, Haxhiu-Poskurica B, Carlo WA: Regulation of expiratory muscles during postnatal development in anesthetized piglets. J Appl Physiol 74:2655-2660, 1993.

Haxhiu-Poskurica B, Ernsberger P, Haxhiu M, Miller M, Cattarossi L, Martin RJ: Development of cholinergic innervation and muscarinic receptor subtypes in piglet trachea. Am J Physiol (Lung Cell Mol Physiol) 264:L606-L614, 1993.

Dreshaj IA, Martin RJ, Miller MJ, Haxhiu MA: Responses of lung parenchyma and airways to tachykinin peptides in piglets. J Appl Physiol 77:147-151, 1994.

Martin RJ, Dreshaj I, Miller M, Haxhiu MA: Hypoglossal and phrenic responses to central respiratory inhibition in piglets. Respir Physiol 97:93-103, 1994.

Litmanovitz I, Dreshaj I, Miller MJ, Haxhiu MA, Martin RJ: Central chemosensitivity affects respiratory muscle responses to laryngeal stimulation in the piglet. J Appl Physiol 76:403-408, 1994.

Martin RJ: Developmental biology and pharmacology of airway function in early childhood asthma: What are the questions? Am J Respir Crit Care Med 151:S9-10, 1995.

Martin RJ, Dreshaj IA, Miller MJ, Haxhiu MA: Neurochemical control of tissue resistance in piglets. J Appl Physiol 79:812-817, 1995.

Cattarossi L, Haxhiu-Poskurica B, Haxhiu MA, Litmanovitz I, Martin RJ, Carlo WA: Carotid bodies and ventilatory response to hypoxia in aminophylline-treated piglets. Pediatr Pulmonol 20:94-100, 1995.

England SJ, Miller MJ, Martin RJ: Unique issues in neonatal respiratory control. IN: Dempsey JA, Pack AI (eds) Regulation of Breathing: Lung Biology in Health and Disease Series, 2nd ed Marcel Dekker, New York, NY, 1995.

Dimaguila MAVT, DiFiore JM, Martin RJ, Miller MJ: Characteristics of hypoxemic episodes in intubated very low birthweight infants. J Pediatr 130:577-583, 1997.

Potter CF, Dreshaj IA, Haxhiu MA, Stork EK, Chatburn RL, Martin RJ: Effect of exogenous and endogenous nitric oxide (NO) on the airway and tissue components of lung resistance in the newborn piglet. Pediatr Res 41:886-891, 1997.

Agani FH, Kuo N-T, Chang C-H, Dreshaj IA, Farver CF, Krause JE, Ernsberger P, Haxhiu MA, Martin RJ: Effect of hyperoxia on substance P expression and airway reactivity in the developing lung. Am J Physiol (Lung Cell Mol Physiol 17):L40-L45, 1997.

Jakupaj M, Martin RJ, Dreshaj IA, Potter CF, Haxhiu MA, Ernsberger P: Role of endogenous nitric oxide in modulating airway contraction mediated by muscarinic receptors during development.Am J Physiol 273 [Lung Cell Mol Physiol 17]:L-531-L536, 1997.

Brooks LJ, DiFiore JM, Martin RJ, and the CHIME Study Group: Assessment of tidal volume over time in preterm infants using respiratory inductance plethysmography. Pediatr Pulmonol 23:42-433, 1997.

Dreshaj IA, Haxhiu MA, Martin RJ: Role of medullary raphé nuclei in the respiratory response to CO_2. Respir Physiol 111:15-23, 1998.

Martin RJ, DiFiore JM, Jana L, Davis RL, Miller MJ, Coles SK, Dick TE: Persistence of the biphasic ventilatory response to hypoxia in preterm infants. J Pediatr 132:960-964, 1998.

Mhanna MJ, Dreshaj IA, Haxhiu MA, Martin RJ: Mechanism for substance P-induced relaxation of precontracted airway smooth muscle during development. Am J Physiol 276 [Lung Cell Mol Physiol 20]: L51-L56, 1999.

Potter CF, Kuo N-T, Farver CF, McMahon JT, Chang C-H, Agani FH, Haxhiu MA, Martin RJ: Effects of hyperoxia on nitric oxide synthase expression, nitric oxide activity, and lung injury in rat pups. Pediatr Res 45:8-13, 1999.

Kuo N-T, Benhayon D, Przybylski RJ, Martin RJ, LaManna JC: Prolonged hypoxia increases vascular endothelial growth factor mRNA and protein in adult mouse brain. J Appl Physiol 86:260-264, 1999.

Mhanna MJ, Dreshaj IA, Haxhiu MA, Martin RJ: Mechanism for substance P-induced relaxation of precontracted airway smooth muscle during development. Am J Physiol 276 [Lung Cell Mol Physiol 20]: L51-L56, 1999.

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Ricardo J. Rodriguez, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Juan J. Paso College, Buenos Aires, Argentina, SA	B.S.	1974	
Univ of Buenos Aires Sch Med, Argentina, SA	M.D.	1980	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1994-1996 Staff Pediatrician & Associate Director, Su Clinica Familiar, Harlingen, TX
1994-1996 Medical Director, Newborn Nursery, Valley Baptist Med Ctr, Harlingen, TX
1996-1998 Director, Division of Neonatology, Mt. Sinai Medical Center, Cleveland, OH
1996-present Assist Prof, Pediatrics, Case Western Reserve Univ Sch Medicine, Cleve, OH
1998-present Director, Neonatal Services, UHHS Geauga Regional Hospital, Chardon, OH
1998-present Medical Director, Neonatal Nurse Practitioners, Rainbow Babies & Childrens Hospital, Cleveland, OH

AWARDS

1990 Honorable Mention, Outstanding Research During Residency Training, American Academy of Pediatrics
2000 "Pearl" of Education, Pearl Day 2000, Rainbow Babies & Children's Hospital, Cleveland, OH

PUBLICATIONS

Riggs TW, Rodriguez RJ, Snider AR, Batton DG: Doppler echocardiographic evaluation of right and left ventricular diastolic function in normal neonates. J Am Coll Cardiol 13:700-705, 1989.

Rodriguez RJ, Riggs TW: Physiologic peripheral pulmonic stenosis in infancy. Am J Cardiol 66:1478-1481, 1990.

Rodriguez RJ, Martin RJ et al: Maturation of the cholinergic responses of tracheal smooth muscle in the piglet. Pediatr Pulmonol 18:28-33, 1994.

Rodriguez RJ, Martin RJ: Exogenous surfactant therapy in newborns. Resp Clin N Am 5:595-616, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Cynthia F. Bearer, Ph.D., M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Smith College, Massachussets	B.A.	1972	Mathematics
Case Western Reserve University, Ohio	Ph.D.	1977	Biochemistry
Johns Hopkins University, Maryland	M.D.	1982	Medicine
Baylor College of Medicine	Postdoctoral	1977-1978	Cell Biology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1982-1983 Intern, Pediatrics, The Johns Hopkins Hospital, Baltimore, MD
1983-1984 Resident, Pediatrics, The Johns Hopkins Hospital Baltimore, MD
1984-1986 Fellow, Joint Program of Neonatology, Harvard Medical School
1986-1987 Fellow, Division of Newborn Medicine, Washington University School of Medicine
1987-1989 Instructor in Pediatrics, Washington University School of Medicine, St. Louis, MO
1990-1992 Assistant Clinical Professor, Department of Growth and Development, UCSF, San Francisco, CA
1992-1994 Associate Professor, Department of Pediatrics, NEOUCOM, Rootstown, OH
1994-present Assistant Professor, Departments of Pediatrics and Neuroscience, Cleveland, OH

AWARDS AND OTHER PROFESSIONAL ACTIVITIES

1978 Awarded NIH Postdoctoral Research Fellowship #32 HL05873-01
1979 Awarded W. Barry Wood Student Research Fellowship, Johns Hopkins Univ School of Medicine
1980 Awarded Cystic Fibrosis Foundation Student Traineeship #H002-01
1985 Awarded Farley Fellowship, The Children's Hospital, Harvard Medical School
1996 Member, Food Safety Advisory Committee, United States Environmental Protection Agency
1997 Member, Extramural Scientific Advisory Board: Fetal Alcohol Syndrome, NIAAA
1997 Member, Scientific Advisory Board, Environmental Health Committee, United States Environmental Protection Agency
1998 Member, NIAAA Special Emphasis Panel
1998 Temporary Advisor, World Health Organization
1998 Presenter, Interagency Coordinating Committee on Fetal Alcohol Syndrome
1999 NIAAA, Special Review Committee ZAA-BB-3

PEER REVIEWED ARTICLES

Bearer CF, Neet KE: Threonine inhibition of the aspartokinase-homoserine dehydrogenase I of *E. coli*: Threonine binding studies. Biochemistry 17:3512-3516, 1978.

Bearer CF, Neet KE: Threonine inhibition of the aspartokinase-homoserine dehydrogenase I of *E. coli*: Stopped-flow kinetics and the cooperativity of inhibition of the homoserine dehydrogenase activity. Biochemistry 17:3517-3522, 1978.

Bearer CF, Neet KE: Threonine inhibition of the aspartokinase-homoserine dehydrogenase I of *E. coli*: A slow transient and cooperativity of inhibition of the aspartokinase activity. Biochemistry 17:3523-3530, 1978.

Birnbaumer L, Bearer CF, Iyengar R: A two-state model of an enzyme with an allosteric regulatory site capable of metabolizing the regulatory ligand. J. Bio. Chem. 255:3552-3557, 1980.

Bearer CF, Knapp RD, Kaumann AJ, Swartz TL, Birnbaumer L: Iodohydroxy- benzylpindolol: Preparation, purification, localization of its iodine to the indole ring, and characterization as a partial agonist. Mol. Pharmacol. 17:328-338, 1980.

Bearer CF, Chang LK, Rosenfeld GC, Thompson WJ: Histamine stimulation of rat gastric parietal cell adenyl cyclase: Modulation by guanine nucleotides. Arch Bioc Bioph 207:325-336, 1981.

Gropper R, Brandt RA, Elias S, Bearer CF, Mayer A, Schwartz AL, Ciechanover A: The ubiquitin-activating enzyme, El, is required for stress-induced lysosomal degradation of cellular proteins. J Biol Chem 266:3602-3610, 1991.

Bearer CF, Gould S, Emerson R, Kinnunen P, Cook CS: Fetal alcohol syndrome and fatty acid ethyl esters. Pediatrics Res 31:492-495, 1992.

Bearer CF, Phillips R: Pediatric environmental health training: Impact on resident behavior. AJDC 147:682-684, 1992.

Bearer CF: EMF and infant incubators. Arch Env Hlth 49:352-354, 1994.

Bearer CF, Emerson RK: Fetal activity of fatty acid ethyl ester synthases. Research Communication in Alcohol and Substances of Abuse 16 (4):189-194, 1995.

Crump C, Bearer CF, Paschal DC, Rodenbaugh D, Etzel RA: Mercury exposure in high school chemistry teachers. Arch Environ Contam Toxicol 31:206-209, 1996.

Bearer CF, Emerson RK, Roitman ES, Shackleton C: Maternal tobacco smoke exposure and persistent pulmonary hypertension of the newborn. Environ Health Perspect 105:202-206, 1997.

Horowitz RS, Dart RC, Jarvie DR, Bearer CF, Gupta U: Placental transfer of N-acetylcysteine following human maternal acetaminophen toxicity. Clin Toxicol 35:447-51, 1997.

Bearer CF: Biomarkers in pediatric environmental health: A cross-cutting issue. Environ Health Perspect. 06(Suppl 3):813-816, 1998.

Bearer CF, Lee S, Salvator AE, Minnes S, Swick A, Yamashita T, Singer L: Ethyl linoleate in meconium: A biomarker for prenatal ethanol exposure. Alcohol Clin Exp Res 23:487-493, 1999.

Bearer CF, Swick AR, O'Riordan MA, Cheng G: Ethanol inhibits L1 mediated neurite outgrowth in postnatal day 6 cerebellar granule cells. J Biol Chem 274:13264-80, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Jalal M. Abu-Shaweesh, M.D.	Instructor, Dept. of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Jordan, Amman, Jordan	M.B.B.S.	1989	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

TRAINING

1989-1990	Rotating Internship, Jordan University Hospital, Amman, Jordan
1990-1992	Obstetrics/Gynecology Residency, Jordan University Hospital, Amman, Jordan
1992-1993	Pediatric Internship, University of Iowa Hospitals & Clinics, Iowa City, IA
1993-1995	Pediatric Residency, University of Iowa Hospitals & Clinics, Iowa City, IA
1995-1999	Neonatal/Perinatal Medicine Fellowship, Division of Neonatology, Rainbow Babies & Childrens Hospital, Cleveland, Ohio
1999	Instructor, Dept. of Pediatrics, School of Medicine, Case Western Reserve University
1999	Attending, Division of Neonatology, Rainbow Babies and Children's Hospital

HONORS AND AWARDS

1991	First place ranked resident, Department of Obstetrics/Gynecology, Jordan University Hospital, Amman, Jordan
1992	First place ranked resident, Department of Obstetrics/Gynecology, Jordan University Hospital, Amman, Jordan
1997	Science Day Presentation Award, Rainbow Babies & Childrens Hospital, Cleveland, OH
1999	Science Day Presentation Award, Rainbow Babies & Childrens Hospital, Cleveland, OH

PUBLICATIONS

Abu-Shaweesh JM, Dreshaj IA, Thomas A, et al: Changes in respiratory timing induced by hypercapnia in maturing rats. Journal of Applied Physiology, 87: 484-490, 1999.

Dreshaj IA, Haxhiu MA, **Abu-Shaweesh JM**, et al: CO_2-induced prolongation of expiratory time during early development. Respiration Physiology, 116(2-3): 125-132, 1999 .

ABSTRACTS [*presentations]

***Abu-Shaweesh J**, Thomas A, Haxhiu M et al: Maturation of ventilatory response to hypoxia, hypercapnia, and combined hypoxia and hypercapnia in rats. Pediatr Res 41:A1446, 1997. [presented at Society for Pediatric Research Annual Meeting (May '97) and Rainbow Babies & Childrens Hospital Science Day (June '97)]

*DiFiore J, Martin RJ, Dreshaj I, **Abu-Shaweesh J**, Neuman M, Adams JA: Peak acceleration of respiratory waveform at onset of inspiration: A new non-invasive measure of respiratory drive. Pediatr Res 41:A1490, 1997. [Presented at Society for Pediatric Research Annual Meeting (May 1997)].

*Abu-Shaweesh J, Dreshaj IA, Haxhiu MA, Martin RJ. (1998). The effect of respiratory timing on maturation of the hypercapnic response in rats. Abstract, Am J Resp Crit Care Med 157:A338, 1998.[Presented at American Thoracic Society Annual Meeting (April 1998)].

*Dreshaj IA, Haxhiu MA, Belegu R, **Abu-Shaweesh J**, Martin RJ. (1998). Brainsrem GABAergic pathways are involved in hypercapnia-induced prolongation of expiratory time (TE) during development. Abstract, Am J Crit Care Med 157:A340, 1998. [Presented at American Thoracic Society Annual Meeting (April 1998)].

*Dreshaj IA, **Abu-Shaweesh J**, Belegu R, Carey RE, Haxhiu MA, Martin RJ. (1998). Hypercapnia induces centrally mediated prolongation of expiratory time in early postnatal life in rats. Pediatr Res 43:281A, 1998. [Presented at Society of pediatric research Annual Meeting (May 1998)].

***Abu-Shaweesh JM**, Dreshaj IA, Haxhiu MA, Martin RJ. An inhibitory role for caudal medullary neurons in hypercapnia-induced prolongation of expiratory duration. Abstract (in press) Am J Crit Care Med, 1999. [Presented at American Thoracic Society Annual Meeting (April 1999)].

*Dreshaj IA, **Abu-Shaweesh JM**, Haxhiu MA, Martin RJ. Hypercapnic loading induces prolongation of early and late expiratory phases in decerebrate piglets during development. Abstract, Am J Crit Care Med, 1999. [Presented at American Thoracic Society Annual Meeting (April 1999)].

***Abu-Shaweesh JM,** Dreshaj IA, Miller MJ, Haxhiu MA, Martin RJ. GABAergic mechanisms are involved in respiratory depression induced by laryngial nerve stimulation. Abstract, Pediatr Res,45: A1723 1999. [Presented at Society for Pediatric Research Annual Meeting (May 99)].

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Terry M. Baird, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Case Western Reserve University, Cleveland, Ohio	B.A	1979	Chemistry
Univ of Cincinnati Coll of Med, Cincinnati, Ohio	M.D.	1983	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1986-1987 Attending Physician, Department of Pediatrics, Michael Reese Hospital and Medical Center, Chicago, IL
1988-1990 Instructor in Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1989-1998 Attending Physician, Division of Neonatology, MetroHealth Medical Center, Cleveland, Ohio
1990-1991 Senior Instructor in Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1991-1998 Assistant Professor of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1998-1999 Fellow in Medical Informatics, University of Utah School of Medicine
1999-present Assistant Professor of Pediatrics, Case Western Reserve University School of Medicine, Cleve, OH

PUBLICATIONS

Rudolph SA, Baird TM, and Wardell JW: Cyclic AMP receptors and cation fluxes in the turkey erthyrocyte. Molecular Pharmacology 21:503-510, 1982.

Baird TM, Neuman MR: Effect of infant position on breath amplitude measured by transthoracic impedance and strain gauges. Pediatric Pulmonology 10:52-56, 1991.

Baird TM, Paton JB, Fisher DE: Improved oxygenation with prone positioning in neonates: Stability of increased transcutaneous $P0_2$. Journal of Perinatology XI:315-318, 1991.

Baird TM, Goydos JM, Neuman MR: Optimal lead placement for monitoring the ECG and breathing in infants. Pediatric Pulmonology 12(4):247-250, 1992.

Silvestri J, et al and CHIME (Baird TM et al): Assessment of compliance with home cardiorespiratory monitoring in infants at risk of sudden infant death syndrome. Journal of Pediatrics 127:384-8, 1995.

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Pending Publication

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Jill E. Baley, M.D.	Associate Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
DePauw University, Greencastle, IN	B.A.	1969-1972	
Univ of Cincinnati College of Medicine, Cincinnati, OH	M.D.	1976	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1981-1990 Assistant Professor, Dept Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1983-present Assistant Professor, Obstetrics & Gynecology, Case Western Reserve Univ School of Medicine, Cleve, OH
1985-1991 Director of Nurseries, Dept of Obstetrics & Gynecology, University MacDonald Women's Hospital, Cleveland, OH
1990-present Associate Professor, Dept Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
1991-present Director, Intermediate Care Unit/Program for Infants with BPD

PUBLICATIONS

Baley JE, Annable WL, Kliegman RM: Candida endophthalmitis in the premature infant. J Pediatr 98:458-461, 1981.

Baley JE, Ruuskanen O, Miller K, Pittard WB III: The effect of theophylline on the neonatal immune response. Pediatr Res 16:649-652, 1982.

Baley JE, Kliegman RM, Fanaroff AA: Disseminated fungal infections in very low birth weight infants: Clinical manifestations and epidemiology. Pediatrics 73:144-152, 1984.

Baley JE, Kliegman RM, Fanaroff AA: Disseminated fungal infections in very low birth weight infants: Therapeutic toxicity. Pediatrics 73:153-157, 1984.

Baley JE, Kliegman RM, Annable WL, Dahms BB, Fanaroff AA: Torulopsis glabrata sepsis in the low birth weight infant: Presentation as necrotizing enterocolitis and endophthalmitis. Am J Dis Child 138:965-966, 1984.

Baley JE, Schacter B: Mechanisms of diminished natural killer cell activity in pregnant women and neonates. J Immunol 134:3042-3048, 1985.

Baley JE, Kliegman RM, Boxerbaum B, Fanaroff AA: Fungal colonization in the very low birth weight infant. Pediatrics 78:225-232, 1986.

Baley JE, Kliegman RM, Fanaroff AA: Candidiasis and other fungal infections of the neonate. Perinatol/Neonatol 10:21-27, 1986.

Bruce MC, Baley JE, Medvik KA, Berger M: Impaired surface expression of C3bi receptors on neonatal PMNs. Pediatr Res 21:306-311, 1987.

Baley JE, Stork EK, Warkentin PI, Shurin SB: Buffy coat transfusions in neutropenic neonates with presumed sepsis: A prospective, randomized trial. Pediatrics 80:712-720, 1987.

Weissman BM, Foster D, Baley JE: Primary thalamic hemorrhage in a preterm infant. Pediatr Neurol 3:121-122, 1987.

Baley JE, Hancharik S, Rivers A: Observations of a support group for parents of children with severe bronchopulmonary dysplasia. J Develop Behav Pediatr 9:19-24, 1988.

Baley JE, Silverman R: Systemic candidiasis: Cutaneous manifestations in low birth weight infants. Pediatrics 82:211-215. 1988.

Baley JE: Neonatal sepsis: The potential for immunotherapy. Clin Perinatol 15:755-772, 1988.

Baley JE, Stork EK, Warkentin PI, Shurin SB: Neonatal neutropenia: Clinical manifestations, cause and outcome. Am J Dis Child 142:1161-1166, 1988.

Clapp DW, Baley JE, Gerson SL: Gestational age dependent changes in circulating hematopoietic stem cells in newborn infants. J Lab Clin Med 113:422-427, 1989.

Clapp DW, Kliegman RM, Baley JE, Campbell K, Fanaroff AA, Berger M: Use of intravenous immunoglobulin to prevent nosocomial sepsis in low birthweight infants. J Pediatr 115:973-978, 1989.

Kyllonen K, Clapp DW, Kliegman RM, Baley JE, Shenker N, Fanaroff AA, Berger M: Dose and interval of intravenous immunoglobulin required to maintain target levels of immunoglobulin G in low birthweight infants. J Pediatr 115:1013-1016, 1989.

Baley JE, Bruce M, Stork E, Klinger J, Medvik K: Granulocyte transfusions in neonatal and adult rats. J Lab Clin Med 115:283-291, 1989.

Baley JE, Meyers C, Kliegman R, Jacobs M, Blumer J: Pharmacokinetics of Amphotericin B and 5-Fluorocytosine in neonates. J Pediatr 116:791-797, 1990.

Baley JE: Neonatal candidiasis: The current challenge. Clin Perinatol 18:263-280, 1991.

Goldfarb J, Baley J, Vanderbrug-Medendorp S, Seto D, Garcia H, Toy P, Watson B, Gooch M: Comparative study of the immunogenicity and safety of two dosing schedules of Engerix-β hepatitis B vaccine in neonates. J Infect Dis 13:18-22, 1994.

Singer LT, Yamashita TS, Hawkins S, Cairns D, Baley J, Kliegman R: Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. J Pediatr 124:765-771, 1994.

Heggie AD, Jacobs MR, Butler VT, Baley JE, Boxerbaum B: Frequency and significance of isolation of Ureaplasma urealyticum and Mycoplasma hominis from cerebrospinal fluid and tracheal aspirate specimens from low birth weight infants. J Pediatr 124:956-961, 1994.

Furman L, Hack M, Watts C, Borawski-Clark E, Baley J, Amini S, Hook B: Twenty-month outcome of ventilator-dependent, very low birth weight infants born during the early years of dexamethasone therapy. J Pediatr 126:434-440, 1995.

Fanaroff AA, Baley JE: Use of immunoglobulins for the prevention of serious infections in premature neonates. Neonatal Monitor 11:2-5, 1995.

Furman L, Baley J, Borawski-Clark E, Hack M: The spectrum of hospitalizations among very low birthweight infants with chronic lung disease. J Pediatr 128:447-452, 1996.

Singer L, Davillier M, Preuss L, Szekely L, Hawkins S, Yamashita T, Baley J: Feeding interactions in infants with very low birthweight and bronchopulmonary dysplasia. J Dev Behav Pediatr 17:69-76, 1996.

The PREVENT Study Group: Reduction of RSV hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 99:93-99, 1997.

Singer L, Yamashita T, Lillien L, Collin M, Baley J: A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. Pediatrics 100:987-993,1997.

Singer LT, Salvator A, Guo S, Collin M, Lilien L, Baley J: Maternal psychological distress and parenting stress after the birth of a very low birth weight infant. JAMA 281:799-805, 1999.

Pending Publication

BIOGRAPHICAL SKETCH

Give the following information for the key personnel, consultants, and collaborators listed on page 4.

NAME	POSITION TITLE
Claire M. Doerschuk	Associate Professor of Physiology and Cell Biology

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Wellesley College, Wellesley, MA	B.A.	1976	Mathematics
Rush University, Chicago, IL	M.D.	1981	Medicine
University of Chicago, Chicago, IL	Certification	1985	Pathology
University of British Columbia, Pulmonary Research Laboratory, Vancouver, BC	Fellowship	1988	Experimental Pulmonary Pathology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE:

1988-1991 Assistant Professor of Pathology, University of British Columbia, Vancouver, BC

1991-1995 Associate Professor of Pediatrics, Pathology and Anatomy, Indiana University, Indianapolis, IN

1995-1999 Associate Professor of Physiology and Cell Biology, Harvard School of Public Health, Boston, MA
Associate Professor of Pathology, Harvard Medical School, Boston, MA

1999- Professor of Pediatrics, Vice-chair of Research, Chief of Division of Integrative Biology, Case Western Reserve University, Cleveland, OH

AWARDS: American Thoracic Society Recognition Award for Scientific Accomplishment - 1998
American Society of Clinical Investigation - 1998
Henry Pickering Bowditch Lectureship, American Physiological Society, Experimental Biology, March, 1993
American Lung Association Career Investigator Award, July, 1990 - 1995

MANUSCRIPTS (94 total)

1. Doerschuk, C.M., R.K. Winn, H.O. Coxson, and J.M. Harlan. CD18-dependent and -independent mechanisms of neutrophil adherence in the pulmonary and systemic microvasculature of rabbits. J. Immunol. 114:2327-2333, 1990.
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3. Doerschuk, C.M. The role of CD18-mediated adhesion in neutrophil sequestration induced by infusion of activated plasma in rabbits. Am. J. Respir. Cell Mol. Biol. 7:140-148, 1992.
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5. Doerschuk, C.M., N. Beyers, H.O. Coxson, B. Wiggs, and J.C. Hogg. Comparison of neutrophil and capillary diameters and their relation to neutrophil sequestration in the lung. J. Appl. Physiol. 74:3040-3045, 1993.
6. Wiggs, B.R., D. English, W.M. Quinlan, N.A. Doyle, J.C. Hogg, and C.M. Doerschuk. The contributions of capillary pathway size and neutrophil deformability to neutrophil transit through rabbit lungs. J. Appl. Physiol. 77:463-470, 1994.
7. Burns, A.B., F. Takei, C.M. Doerschuk. ICAM-1 expression in mouse lung during pneumonia. J. Immunol. 153:3189-3198, 1994.
8. Doerschuk, C.M., J. Markos, H.O. Coxson, D. English, and J.C. Hogg. Quantitation of neutrophil migration in acute bacterial pneumonia in rabbits. J. Appl. Physiol. 77:2593-2599, 1994.
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12. Pavalko, F.M., D.M. Walker, L. Graham, M. Goheen, C.M. Doerschuk, and G.S. Kansas. The cytoplasmic domain of L-selectin interacts with cytoskeletal proteins via α-actinin: receptor positioning in microvilli does not require cytoskeletal associations. J. Cell Biol. 129:1155-1164, 1995.
13. Kumasaka, T., N.A. Doyle, W.M. Quinlan, L. Graham, and C.M. Doerschuk. The role of CD11/CD18 in neutrophil

emigration during acute and recurrent *Pseudomonas aeruginosa*-induced pneumonia in rabbits. Am. J. Pathol. 148:1297-1305, 1996.

14. Bullard, D.C., E.J. Kunkel, H. Kubo, M.J. Hicks, I. Lorenzo, N.A. Doyle, C.M. Doerschuk, K. Ley, and A.L. Beaudet. Infectious susceptibility and severe deficiency of leukocyte rolling and recruitment in E-selectin and P-selectin double mutant mice. J. Exp. Med. 183:2329-2336, 1996.
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17. Kumasaka, T., W.M. Quinlan, N.A. Doyle, T.P.E. Condon, J. Sligh, F. Takei, A.L. Beaudet, C.F. Bennett, and C.M. Doerschuk. The role of ICAM-1 in endotoxin-induced pneumonia evaluated using ICAM-1 antisense, anti-ICAM-1 antibodies, and ICAM-1 mutant mice. J. Clin. Invest. 97:2362-2369, 1996.
18. Mizgerd, J.P., B.B. Meek, G.J. Kutkoski, D.C. Bullard, A.L. Beaudet, and C.M. Doerschuk. Selectins and neutrophil traffic: margination and *Streptococcus pneumoniae*-induced emigration in murine lungs. J. Exp. Med. 184:639-645, 1996.
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36. Pending Publication
37. Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Musa A. Haxhiu	Professor, Pediatrics, Medicine and Anatomy

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Belgrade	M.D.	1963	
University of Belgrade	Mr. Sc	1971	
University of Zagreb	Ph.D.	1973	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1964-1968	Hospital for Lung Diseases, Peje, Kosova, Yugoslavia (Intern)
1966-1971	Institute for Lung Disease and TBC, Belgrade, Yugoslavia (Resident)
1973	Postgraduate Medical School, London, England (Visiting lecturer)
1973-1975	Dean, Medical Faculty, University of Prishtina, Prishtina, Yugoslavia.
1975-1976	University of Pennsylvania, Philadelphia, PA, Visiting Scientist, Fulbright Program.
1978, 1980	Silikose-Forschungsinstitut der Bergbau-Berufsgenossenschaft Bochum, West Germany (Visiting Scientist)
1981-1982	Case Western Reserve University, Cleveland, Ohio, Visiting Professor
1983-1987	Professor of Clinical Physiology, Institute of Clinical Physiology.
1987-1990	Case Western Reserve University, Visiting Professor.
1987	Cardiovascular Research Institute, Medical School, San Francisco, visiting scientist
1989-1990	Department of Pharmacology, University of the Health Sciences, Bethesda, Maryland, Visiting Scientist
1983-1990	Professor of Clinical Physiology, Medical Faculty, University in Prishtina, Yugoslavia.
1990-1991	Visiting Professor of Medicine, Case Western Reserve University, Cleveland, Ohio. President of Academy of Sciences and Arts of Kosova.
1992-present	Professor of Medicine, Case Western Reserve University, Cleveland, OH

SELECTED PUBLICATIONS (from a total of 212)

Haxhiu MA, Erokwu BO, Cherniack NS: The brainstem network involved in coordination of inspiratory activity and cholinergic outflow to the airways. J Autonomic Nerv System 1996; 61(2):155-161.

Haxhiu MA, Loewy AD: Central connections of the motor and sensory vagal systems innervating the trachea. J Autonomic Nerv System 1996; 57:49-56.

Dreshaj IA, Haxhiu MA, Potter CF, Agani FH, Martin RJ: Maturational changes in responses of tissue and airway resistance to histamine. J Appl Physiol, 1996; 81(4):1785-179.

Haxhiu MA, Yung K, Erokwu B, Cherniack NS: CO_2-induced c-fos expression in the CNS catecholamingeric neurons. Respir Physiol 1996; 105(1-2):35-45.

Potter CF, Dreshaj IA, Haxhiu MA, Stork EK, Chatburn RL, Martin RJ: Effect of exogenous and endogenous nitric oxide on airway and tissue components of lung resistance in the newborn piglet. Pediatr Res 1997; 41(6):886-891.

Sahin M, Haxhiu MA, Durand DM, Dreshaj IA: Spiral nerve cuff electrode for recordings of respiratory output. J Appl Physiol 1997; 83:317-322.

Agani FH, Kuo N-T, Chang C-H, Dreshaj IA, Farver CF, Krause JE, Ernsberger P, Haxhiu MA, Martin R: Effect of hyperoxia on substance P expression and airway reactivity in the developing lung. Am J Physiol 273 (Lung Cell Mol Physiol 17):1997; L40-L45.

Ernsberger P, Haxhiu MA: The I1-imidazoline binding site is a functional receptor mediating vasodepression via the ventral medulla. Am J Physiol 1997; 273 (Regulatory Integrative Comp. Physiol. 42):R1572-R1579.

Lyubkin M, Durand DM, Haxhiu MA: Interaction between long-term potentiation and hypoxia-induced potentiation in the rat hippocampus. J Neurophysiol 1997; 78:2775, 2782.

Jakupaj M, Martin RJ, Dreshaj IA, Potter CF, Haxhiu MA, Ernsberger P: Role of endogenous NO in modulating airway contraction mediated by muscarinic receptors during development. Am J Physiol 273 (Lung Cell Mol Physiol 1997; 17:531-L536.

Yeh ER, Erokwu B, LaManna JC, Haxhiu MA: The paraventricular nucleus of the hypothalamus influences respiratory timing and activity in the rat. Neurosci Lett 1997; 233:63-66.

Kuo NT, Agani FH, Haxhiu MA, Chang CH: Protein kinase C (PKC) is required for CO_2-induction of c-fos mRNA in PC12 cells. Respir Physiol 1998; 111(2):127-135.

Dreshaj IA, Haxhiu MA, Martin RJ: Role of the medullary raphé nuclei in the respiratory response to CO_2. Respir Physiol 1998; 111(1):15-23.

Haxhiu MA, Erokwu B, Dreshaj IA: The role of excitatory amino acids in airway reflex responses in anesthetized dogs. J Auton Nerv System 1998; 67:192-199.

Haxhiu MA, Erokwu BO, Bhardwaj V, Dreshaj IA: The role of the medullary raphé nuclei in regulation of cholinergic outflow to the airways. J Auton Nerv System 1998; 69:64-71.

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Haxhiu MA, Dreshaj IA, McFadden CB, Erokwu BO, Ernsberger P: I1-imidazoline receptors and cholinergic outflow to the airways. J Auton Nerv Syst 1998; 1(2-30):167-174.

Hall LR, Mehlotra RK, Higgins AW, Haxhiu MA, Pearlman E: An essential role for interleukin-5 and eosinophils in helminth-induced airway hyperresponsiveness. Infection and Immunity, Sept. 1998; 4425-4430.

Haxhiu MA, Dreshaj IA, McFadden CB, Erokwu, BO, Ernsberger P: I_1-imidazoline receptors and cholinergic outflow to the airways. J Auton Nerv Syst 1998; 71:167-174.

Mhanna MJ, Dreshaj IA, Haxhiu MA, Martin RJ: Mechanism for substance P-induced relaxation of precontracted airway smooth muscle during development. Am J Physiol 276(1 Pt 1):L51-L56, 1999.

Potter CF, Kuo NT, Farver CF, McMahon JT, Chang CH, Agani FH, Haxhiu MA, Martin RJ: Effects of hyperoxia on nitric oxide synthase expression, nitric oxide activity, and lung injury in rat pups. Pediatr Res 1999; 45(1):8-13.

da Neves L, Duchala CS, Godinho F, Haxhiu MA, Colmenares C, Macklin WB, Campbell CE, Butz KG, Gronostajski RM: Disruption of the murine nuclear factor I-A gene (Nfia) results in perinatal lethality, hydrocephalus, and agenesis of the corpus callosum. Proc Natl Acad Sci U.S.A. 1999; 96(21):111946-11951.

Belegu R, Hadžiefendić S, Dreshaj IA, Haxhiu MA, Martin RJ: CO_2-induced c-fos expression in medullary neurons during early development. Respir Physiol 1999; 117(1):13-28.

Dreshaj IA, Haxhiu MA, Abu-Shaweesh J, Carey RE, Martin RJ: CO_2-induced prolongation of expiratory time during early development. Respir Physiol 1999; 116(2-3):125-132.

Grill WM, Erokwu BO, Hadžiefendić S, Haxhiu MA: Extended survival time following pseudorabies virus injection labels the suprapontine neural network controlling the bladder and urethra in the rat. Neurosci Lett 1999; 270(2):63-66.

Abu-Shaweesh JM, Dreshaj IA, Thomas AJ, Haxhiu MA, Strohl KP, Martin RJ: Changes in respiratory timing induced by hypercapnia in maturing rats. J Appl Physiol 1999; 87(2):484-490.

Hadžiefendić S, Haxhiu MA: CNS innervation of vagal preganglionic neurons controlling peripheral airways: a transneuronal labeling study using pseudorabies virus. J Auton Nerv Syst 1999; 76(2-3):135-145.

Patil MM, Durand DM, LaManna JC, Whittingham TS, Haxhiu MA: Effects of oxygen deprivation on parapyramidal neurons of the ventrolateral medulla in the rat. Respir Physiol 1999; 115(1):11-22.

Potter CF, Kuo NT, Farver CF, McMahon JT, Chang CH, Agani FH, Haxhiu MA, Martin RJ: Effects of hyperoxia on nitric oxide synthase expression, nitric oxide activity, and lung injury in rat pups. Pediatr Res 1999; 45(1):8-13.

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Sahin M, Durand DM, Haxhiu MA: Chronic recordings of hypoglossal nerve activity in a dog model of upper airway obstruction. J Appl Physiol, in press, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Susan D. Izatt, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Massachusetts Inst of Technology, Cambridge, MA	SB	1983	Chemical Engineering
Tufts University School of Medicine, Boston, MA	MD	1987	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1988- 990 Clinical Fellow in Pediatrics, Tufts, Boston, Massachusetts
1990-1994 Clinical Fellow in Pediatrics, Harvard, Boston, Massachusetts
1993-1994 Associate Neonatologist, Joint Program in Neonatology, Beth Israel Hospital, Brigham and Women's Hospital, The Children's Hospital, Boston, Massachusetts
1993-1994 Associate Neonatologist, Winchester Hospital, Winchester, M.A.
1994-1995 Staff Neonatologist, St. Lukes Medical Center, Cleveland, Ohio
1994-1995 Director of Newborn Services, St. Lukes Medical Center, Cleveland, Ohio
1995-present Assistant Professor, Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital, Cleveland, Ohio

PUBLICATIONS

Izatt SD: Breastfeeding counseling by health care providers. J Hum Lact 13:109-113, 1997.

Mhanna MJ, Bennet JB II, Izatt SD: Potential fluoxetine chloride (Prozac) toxicity in a newborn. (Letter to the Editor). Pediatrics 100:158-159, 1997.

BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Nancy E. Judge, M.D.	Assistant Professor, Reproductive Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Smith College	B.S.	1973	AB Psychology
University of Massachusetts	M.D.	1977	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1981-1990 Full-Time Attending Staff, Dept Obstetrics/Gynecology, Case Western Reserve University School of Medicine, Cleveland Metropolitan General Hospital, Cleveland, OH

1981 Assistant Professor of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, OH

1990-present Director, Prenatal Diagnostics Center, Dept Obstetrics/Gynecology, University MacDonald Women's Hospital, Cleveland, OH

AWARD

1990 MetroHealth Medical Center Department of Ob/Gyn Teaching Award

1991 Charles H. Hendricks, M.D. Teaching Award in Recognition of Outstanding Commitment to Resident Education (Full-Time Faculty)

1994 Council on Resident Education in Obstetrics and Gynecology National Faculty Award for Excellence in Resident Education

PUBLICATIONS

Bottoms S, Judge NE, Kuhnert P, Sokol RJ: Thiocyanate and drinking during pregnancy. Alcoholism: Clinical and Experimental Research 6:3, 1982.

Jorenson RU, Tomford JW, Gyves MT, Judge NE, Colmar SH: Use of intravenous immune globulin in pregnant women with common variable hypoammoglobulinemia. Proceedings of a symposium: Intravenous immune globulin and the compromised host, Good RA (ed), AJM March 30, 1984, 73-82.

Judge NE, Mann LI, Lupe P, Amini S: Clinical associations of variable decelerations during reactive non-stress tests. Obstet Gynecol 74:351-6, 1989.

Al-Malt A, Ashmead G, Judge N, Mann L, Ashmead J, Stepanchak W: Color-flow and doppler velocimetry in prenatal diagnosis of acardiac triplet. J Ultra Med 10:341-45, 1991.

Johnson CE, Elder JS, Judge NE, Adeeb FN, Grisoni ER, Fattlar DC: The accuracy of antenatal sonography in identifying renal abnormalities. AJDC 146:1181-84, 1992.

Patel CR, Judge NE, Muise KL, Levine MM: Prenatal myocardial infarction suspected by fetal echocardiology. J Am Soc Echocardiogr 9:721-3, 1996.

Robin NH, Ko LM, Heeger S, Muise KL, Judge NE, Bangert BA: Syntelencephaly in an infant of a diabetic mother. Am J Hum Gen 66:433-437, 1996.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Robert Kiwi, M.D.	Associate Professor, Reproductive Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Cape Town, South Africa	MB, BCh	1968	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1977-1980 Fellow, Perinatal Medicine, University MacDonald Women's Hospital, Cleveland, Ohio
1980-1989 Chief, Division of Obstetrics, The Mt. Sinai Medical Center, Cleveland, Ohio
1980-1990 Assistant Professor, Reproductive Biology, Case Western Reserve Univ Sch Med, Cleveland, OH
1990-present Associate Professor, Reproductive Biology, Case Western Reserve University, Cleveland, Ohio
1990-present Chief, Division of Obstetrics, University MacDonald Women's Hospital, Cleveland, Ohio

AWARD

1998 CREOG Award: National Faculty Award for Excellence in Resident Education

PUBLICATIONS

Sher J, Kiwi R, Baillie P: Use of prostaglandin E2 in the management of intrauterine deaths. Suppl. to South African Medical Journal, Oct. 16, 1974.

Franks S, Kiwi R, Nabarro JDN: Pregnancy and lactation after pituitary surgery. Br Med J, 822, 1977.

Kiwi R: Colposcopy - a year's experience and results (1977-1978): Proceedings of the Victor Bonney Society, June, 1978.

Parulekar SG, Kiwi R: Ultrasound evaluation of sutures following cervical cerclage for incompetent cervix uteri. J Ultra Med 1:223-228, 1982.

Sheean LA, Utian WH, Goldfarb JM, Kiwi R: In vitro fertilization of human oocytes as related to morphology of the cumulus oophorus, serum estradiol, pelvic ultrasound, and day of embryo replacement. Abstract Fertil & Steril, 41:555, 1984.

Sheean LA, Goldfarb JM, Kiwi R, Utian WH: Potential contamination of IVF culture media by ultrasound directed percutaneous aspiration techniques. Abstract Fifth World Congress on Human Reproduction, September, 1985.

Utian WH. Sheean L. Goldfarb JM. Kiwi R: Successful pregnancy after in vitro fertilization and embryo transfer from an infertile woman to a surrogate [letter]. New Engl J of Med. 313(21): 1351-1352, 1985.

Sheean LA, Goldfarb JM, Kiwi R, Utian WH: Arrest of embryo development by ultrasound coupling gels. Fertil & Steril, 45:568-571, 1986.

Sheean LA, Goldfarb JM, Kiwi R, Utian WH: Isolation of motile sperm from oligospermic and asthenospermic semen samples: Simple washing versus density gradient centrifugation. Proceedings of The Fifth World Congress - In Vitro Fertilization and Embryo Transfer, p. 141, 1987.

Sheean LA, Goldfarb JM, Kiwi R, Utian WH: Preparation for intrauterine insemination (IUI) using Percoll. Proceedings of The Annual Meeting of The American Fertility Society, p. 40, 1987.

Kiwi R, Newman MR, Merkatz IR: Determination of the elastic properties of the cervix. Obstet & Gynecol, 71:4, 1988.

Parulekar SG, Kiwi R: Dynamic incompetent cervix uteri: Sonographic observations. J Ultra Med, 7:481-485, 1988.

Kiwi R, Utian WH: Obstetrical risk of pregnancy and childbirth after age 35. Maturitas, Supp. 1, 1988, p. 63-72.

Sheean LA, Goldfarb JM, Kiwi R, Utian WH: In vitro fertilization (IVF)-surrogacy: Application of IVF to women without functional uterri. J IVF & ET, 6:3, 1989.

Utian WH, Goldfarb JM, Kiwi R, Sheean LA, Auld HV, Lisbona H: Preliminary experience with in vitro fertilization-surrogate gestational pregnancy. Fertil & Steril, 52:4, 1989.

Aszodi A, Ponsky JL, Kiwi R, Parulekar SG: Choledochal cyst in a pregnant adult. Am J Gastroenterology, 85:8, 1990.

Kiwi R: Puerperal infection, Current Therapy in Emergency Medicine. First edition in 1986 and second edition in 1990. Edited by M. Callaham. B.C. Decker, Inc.

Kliegman RM, Madura D, Kiwi R, Eisenberg I, Yamashita T: The relationship of maternal cocaine use with the risks of prematurity and low birthweight. J Pediatr, 124:751-6, 1994.

Hook B, Kiwi R, Muise K, Amini S, Fanaroff A, Pollack S, Izanec J, Hack M: Trial of labor after Cesarean section: Implications for the mother and infant. Am J Obstet Gynecol, 172:296, 1995.

Hook B, Kiwi R, Amini SB, Fanaroff A, Hack M: Neonatal morbidity after elective repeat cesarean section and a trial of labor. Pediatrics 100:348-353, 1997.

Chidiac RM, Madhun ZT, Taylor H, Kiwi R, Judge N, Arafat B, Schulak J, Aron DC: Primary hyperpathyroidism in pregnancy: a retrospective analysis. 79th Annual Meeting of the Endocrine Society, February 1997.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Kevin L. Muise, M.D.	Assistant Professor, Reproductive Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Lowell, Lowell, Massachusetts	B.S.	1981	Biology
Boston University School of Medicine	M.D.	1986	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1990-1992 Instructor, Dept Reprod Biol, Case Western Reserve University School of Medicine, Cleveland, Ohio
1992-present Assist Prof, Dept Reprod Biol, Case Western Reserve University School of Medicine, Cleveland, Ohio
1993-present Assist Prof, Dept Fam Med, Case Western Reserve University School of Medicine, Cleveland, Ohio

AWARD

1996 American Academy of Family Physicians Teaching Award
1997 University Hospitals Mount Sinai Residency Director's Award for Outstanding Achievement
1997 CREOG National Faculty Award for Excellence in Resident Education

PUBLICATIONS

Ridgway LE, Muise KL, Wright JW, Patterson RM, Newton ER, Gibbs RS: A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. Am J Obstet Gynecol 163:879-82, 1990.

Muise KL, Duchon MA, Brown RH: Effect of angular traction on the performance of modern vacuum extractors. Am J Obstet Gynecol 167:1125-9, 1992.

Muise KL, Duchon MA, Brown RH: The effect of artificial caput on performance of vacuum extractors. Obstet Gynecol 81:170-3, 1993.

Duchon MA, Muise KL: Pregnancy after age 35. The Female Patient 18:69-72, 1993.

Duchon MA, Muise KL: Pregnancy after age 35. Physician Assistant 17:27-36, 1993.

Muise KL, Duchon MA: Effect of angular traction on the performance of modern vacuum extractors: letter to the editor. Am J Obstet Gynecol 169:748-9, 1993

Patel CR, Muise KL, Levine MM: Prenatal diagnosis of an obstructive mediastinal bronchogenic cyst. Cardiol Young 5:194-5, 1995.

Wiper DA, Duchon MA, Muise KL: Vacuum sources in obstetrics. J Repro Med 41:442-6, 1996.

Robin NH, Ko LM, Heeger S, Muise KL, Judge N, Bangert BA: Syntelencephaly in an infant of a diabetic mother. Am J Med Genet 1996.

Loret de Mola JR, Muise KL, Duchon MA: Porpyria cutanea tarda and pregnancy. Obstet Gynecol Surv 51:493-7, 1996.

Patel CR, Judge NJ, Muise KL, Levine MM: Prenatal myocardial infarction suspected by fetal echocardiography. J Am Soc Echocardiogr 9:721-3, 1996.

Robin NH, Ko LM, Heeger S, Muise KL, Judge NE, Bangert BA: Syntelencephaly in an Infant of a Diabetic Mother. Am J Med Gen 66:433-437, 1996.

Alemi F, Stephens RC, Muise K, Dyches H, Mosavel M, Butts J: Educating patients at home: Community Health Rap Medical Care Suppl, 34:OS21-OS31, 1996.

Loret de Mola JR, Judge NE, Entsminger C, Deviney M, Muise KL: Indirect prediction of fetal lung maturity: value of

ultrasonographic colonic and placental grading. J Repro Med 43:898-902.

Patel CR, Muise KL, Redline R: Double-outlet right ventricle with intact intraventricular septum in a foetus with trisomy-18. Cardiol Young 9:419-422, 1999.

Muise KL, Judge NE, Morrison SC: Perinatal ultrasound. In: Martin RJ and Fanaroff AA [eds]: *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant* (Vol. 1, 6th edition) St. Louis: Mosby-Year Book, Inc. 1997:84-108.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Nancy S. Newman, B.A., R.N.	Research Nurse

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Bay Path Jr Coll, Longmeadow, MA	AS	1971	Pre-Nursing
Geo Washington Univ, Washington, DC	BA	1973	Sociology
Washington Hosp Cntr Sch Nursing, Washington, DC	Diploma	1978	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1978-1983 Staff Nurse, Neonatal Intensive Care Unit, Washington Hospital Center, Washington, DC
1984-1985 Head Nurse, Reg Neonatal Intensive Care Unit, Children's Hospital Med Cntr of Akron, Akron, OH
1985-1986 Staff Nurse, Newborn Nursery, Marymount Hospital, Garfield Hts., OH
1986-present Clinical Research Coordinator, Division of Neonatology, Case Western Reserve Univ, Rainbow Babies & Children's Hospital, Cleve, OH

PUBLICATIONS

Skidmore MD, Shenker N, Kliegman RM, Shurin S, Allen R: Biochemical evidence of vitamin B12 deficiency in asymptomatic children after ileal resection for necrotizing enterocolitis. J Pediatr 115:102-105, 1989.

Clapp DW, Kliegman RM, Baley JE, Shenker N, Kyllonen K, Fanaroff AA, Berger M: Use of intravenously administered immunoglobulin to prevent nosocomial sepsis in low birthweight infants: Report of a pilot study. J Pediatr 115:973-978, 1989.

Kyllonen K, Clapp DW, Kliegman RM, Baley JE, Shenker N, Fanaroff AA, Berger M: Dosage of intravenously administered immune globulin and dosing interval required to maintain target levels of immunoglobulin G in low birthweight infants. J Pediatr 115:1013-1016, 1989.

Ballance WA, Dahms BB, Shenker N, Kliegman RM: Pathology of neonatal necrotizing enterocolitis: A ten year experience. J Pediatr 117:S6-S13, 1990.

Pappin S, Shenker N, Hack M, Redline RW: Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. J Pediatr 124:621-626, 1994.

Hook B, Hack M, Morrison S, Borawski-Clark E, Newman N, Fanaroff A: Pneumopericardium in very low birthweight infants. J Perinatol 15:27-31, 1995.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Douglas P. Powell, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Georgetown University, Washington, DC	BS	1964	
University of Louisville, Louisville, KY	MD	1968	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1973-1976	Pediatrician, Colorado Permanente Medical Group, Denver, CO
1977-1978	Instructor, Pediatrics, University of Colorado Medical Center, Denver, CO
1977	Director, High Risk Infant Care Course, University of Colorado Medical Center, Denver, CO
1978	Co-Director, High Risk Infant Care Course, University of Colorado Medical Center, Denver, CO
1978-1984	Co-Director, Neonatal Intensive Care, Unit-Bronson Methodist Hospital, Kalamazoo, MI
1984-1989	Chief, Neonatology, St. Peter's Hospital, Albany, NY
1989-1992	Chief, Neonatology, Mt. Sinai Medical Center, Cleveland, OH
1991-present	Consultant in Neonatology, The Cleveland Clinic Foundation, Cleveland, OH
1992-1998	Staff Neonatologist, Mt. Sinai Medical Center, Cleveland, OH
1993-1998	Instructor, Family Practice Resident Program, University Hospitals of Cleveland, Cleveland, OH
1995-present	Senior Clinical Instructor, Family Medicine, Case Western Reserve University Sch Medicine, Cleve, OH
1998-2000	Interim Director, Department of Pediatrics, Mt. Sinai Medical Center, Cleveland, OH
2000-present	Assistant Professor, Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH
2000-present	Assistant Professor, Division of Neonatology, Rainbow Babies & Children's Hospital, Cleveland, OH

PUBLICATIONS

Taylor JF, Pugh [Powell] DP, Benjamin F: Effects of gaseous hydrocarbons on the sedimentation velocity of hemoglobin. Federation Proceedings 25:May-June, 1966.

Lubchenco L, McGuiness G, Tomlinson A, Pugh [Powell] D: Aggressive obstetric neonatal management: Long term outcome. *New Techniques and Concepts in Maternal and Fetal Medicine*. VanNostrand, Reinhold, Series, Litton Publishing, 1979.

Black V, Lubchenco L, Luckey D, Koops B, McGuiness G, Powell D, Tomlinson A: Development and neurologic sequelae of neonatal hyperviscosity syndrome. Pediatrics 69: , 1982.

Black V, Lubchenco L, Koops RL, Poland R, Powell D: Neonatal hyperviscosity: Randomized study of effect on transfusion. Pediatrics 75: , 1985.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Dinesh M. Shah, M.D.	Associate Professor, Reproductive Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Elphinstone College, Bombay	Int. Sc.	1968	Biology
T. National Medical College	M.B., B.S.	1972	Medicine/Surgery
T. National Medical College	M.D.	1976	OB/GYN

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1983-1990 Assist Prof, Maternal-Fetal Med, Dept OB/GYN, Vanderbilt University, Nashville, TN
1990-1993 Assist Prof, Maternal-Fetal Med, Dept OB/GYN, Univ TX Hlth Sci Ctr at San Antonio, Texas
1993-1997 Assoc Prof, Maternal-Fetal Med, Dept OB/GYN, Univ TX Hlth Sci Ctr at San Antonio, San Antonio, TX
1997-present Assoc Prof, Reproductive Biology, Case Western University School of Medicine, Cleve, OH
1997-present Director, Maternal-Fetal Medicine, University MacDonald Women's Hospital, Cleve, OH

AWARDS/HONORS

1990 Italian Society of Perinatal Medicine and Italian Society for Hypertension in Pregnancy on the occasion of VIIth World Congress of Hypertension in Pregnancy - 5th Prize.

PUBLICATIONS

Roberts RM, Shah DM, Jeanty P, Beattie JF: Twin, acardiac, ultrasound-guided embolization. Fetus 1(3):5-10, 1991.

Jeanty P, Sacks GA, Shah DM, Fleischer AC: Prenatal diagnosis of fetal cephalocele: A sonographic spectrum. Am J Perinatol 8:144-149, 1991.

Shah DM, Higuchi K, Inagami T, Osteen KG: Effect of progesterone on renin secretion in endometrial stromal, chorionic trophoblast, and mesenchymal monolayer cultures. Am J Obstet Gynecol 164:1145-1150, 1991.

Worrel JA, Fleischer AC, Drolshagan LF, Durmon GR, Shah DM: Duplex doppler sonographer of the umbilical arteries: Predictive value in IUGR and correlation with birth weight. Ultrasound Med Biol 17:207-210, 1991.

Shah DM, Frazer M, Badr KF: Circulating endothelin-1 is not increased in severe preeclampsia. J Matern Fetal Med 1(4):177-180, 1992.

Shah DM, Shenai JP, Vaughn WK: Neonatal outcome of premature infants of preeclamptic mothers. J Perinatol 7:264-267, 1995.

Sorem KA, Shah DM: Advanced triploid pregnancy and preeclampsia. South Med J 88(11):1144-5, 1995.

Patel CR, Shah DM, Dahms BB: Prenatal diagnosis of a coronary fistula in a fetus with pulmonary artresia with intact ventricular septum and trisomy 18. J Ultrasound Med 18:429-431.

Shah DM, Reed G: Obstetric parameters associated with adverse perinatal outcome in hypertensive pregnancies. J Hum Hypertens 10:511-515, 1996.

Grant WM, Shah DM: Decidual renin secretion is modulated by vascular endothelial cells. J Matern Fetal Med 5:58-63, 1996.

Pending Publication

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Neena D.Shah, M.D.	Assistant Professor, Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Parle College, Bombay, India	Int. Sc.	1971	Biology
T. National Medical College, Bombay India	M.B., B.S.	1976	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1989-1990 Clinical Instructor, Department of Pediatrics, Division of Neonatology, Vanderbilt University, Nashville, Tennessee

1990-1997 Assistant Professor, Department of Pediatrics, Division of Neonatology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

1997 -present Assistant Professor of Pediatrics, CWRU and RB&C Hosp, Cleveland, OH

AWARDS

1993 Kinetic Concepts (3 year grant): "Effects of Continuous Oscillation Therapy in Intubated Neonates", 1993 - 1996 ($92,820)

PUBLICATIONS

Shah N, Lindstrom DP, Cotton RB: Effect of slow infusion of indomethacin (Indo) on cerebral blood flow velocity (CBFV) in preterm infant. Pediatr Res 27:225A, 1990.

OTHER SUPPORT:

AVROY A. FANAROFF, M.D.

NONE

Hack, Maureen

ACTIVE

RO1 HD34177-04 (Hack) 02/01/97-01/31/01 %
NIH $199,431
Young Adult Outcomes of Very Low Birthweight
This is a longitudinal study of outcomes of very low birthweight to examine growth, health and functional outcomes.
Overlap: None

2U10HD21364-11 (Fanaroff) 01/01/96-12/31/01 No salary support
NIH $594,532 TDC
Cooperative Multicenter Network on Neonatal Intensive Care Units
The NICHD Multicenter Network examines neonatal outcomes and performs randomized controlled clinical trials.
Overlap: None

2RO1 NR01894-06A1 (D. Holditch-Davis) 04/01/98-03/31/02 %
NIH $1,653,612
Assessment of Biological and Social Risk in Preterm Infants
The major goal of this study is to examine the predictive validity of neonatal behavior, EEG, and social risk on growth and development during infancy and early childhood.
Overlap: None

PENDING

Pending Support

Pending Support

a:\Hack\Updated CVDiskHack.sup:

% = Percentage of Effort

OTHER SUPPORT:

MICHELE C. WALSH-SUKYS, M.D.

ACTIVE

MSCIDA-NICHI - HD21364-13S1 [Walsh-Sukys] 1998-2000 %
Supplement to NICHD Neonatal Research Network [Fanaroff] $138,308
Neonatal Respiratory Failure Outcome: Impact of Alkalosis

The purpose of this project is to further the knowledge of the impacts of treatment in persistent pulmonary hypertension of the newborn [PPHN], and to serve as a vehicle for training in state-of-the-art techniques of clinical epidemiology including observational research methodology, longitudinal models of outcomes and clinical trial design.

Overlap: None

ACTIVE

Specialized Clinical Investigator Career 1998-2000
Development Award [Walsh-Sukys]
Supplement to NICHD Neonatal Research Network [Fanaroff]
Neonatal Chronic Lung Disease: An Epidemiologic Investigation and Benchmarking Initiative

% = Percentage of Effort

HAXHIU, MUSA A.

ACTIVE (P.I.)

NIH NHLBI HL 50527 (Haxhiu) 7/1/98-6/30/2002 %
Airways-Central Nervous System $989,505
The investigation consists of two complementary lines of research focussed on the same problem: the analysis of CNS control of the airways. The first part deals with neuroanatomy of central airway pathways and the second is focussed on the role of specific CNS regions in these identified pathways on regulation of secretomotor and bronchomotor control.

Solvay Pharma (Haxhiu) 11/30/99-12/01/01 %
$57,000
Bombesin-like peptides and central regulation of cardiorespiratory functions
To define the neuronal network involvedi n medating the physiological changes by activation of bombesin receptor subtype 3 and to determine the role of bomesin receptor subytype 3 in regulation of cardiorespiratory functions.

NO1-NS-5-2331 (W. Grill) 09/30/95-09/29/2001 %
NIH NHLBI $995,387
Microstimulation of lumbo-sacral spinal cord: mapping Proj. 2
Specific aims of project To optimize the spinal nerve cuff geometry specificity for recording from the HG nerve. Next to demonstrate the feasibility of chronic nerve recordings specifically on hypoglossal nerve and develop the signal processing technique for timely detection of apneic events. There is no scientific or budgetary overlap.

RO1 (Dearborn) 9/1/98-8/31/2003 %
Stachybotrys-induced hemorrhage in the developing lung $1,890,674

NIH-NHLBI (Martin) 4/1/99-3/31/2004 %
Respiratory responses to hypercapnia during Development $319,805
We will test the hypothesis that the CO_2-chemosensory system modulates regulation of respiratory timing and accompanying inspiratory and expiratory muscle behavior during postnatal development and that CO_2-induced activation of central inhibitory systems such as GABAergic and $_2$-adrenergic pathways in early life is responsible for the maturational changes in these responses.

Private Support (Haxhiu) 01/01/00-12/31/01 %
Selective inhibition of the Na^+/H^+ exchanger type 3 and respiratory drive $101, 649
To characterize the effects of selective inhibition of Na+/H+ exchange type 3 on activity of upper airway dilating and chest wall pumping muscles on apneic threshold; to examine the effects of selective inhibition of Na+/H+ exchanger type 3 on reflex apnea included by stimulation of pulmonary C-fiber receptors; and to determine the neuronal network involved in mediating ventilatory and cardiovascular response to selective inhibition of Na+/H+ exchanger type 3.

NIH NINDS U54 NS 39407 (Haxhiu) 10/01/99-09/30/04 %
Neuronal and chemical control of breathing $6,963,912 (TDC)
And airways, Haxhiu is Program Director and
PI on Proj. 1 (Howard University)

PENDING

Pending Support

% = Percentage of Effort

Pending Support

OVERLAP: None

If this grant is funded, my effort will be adjusted accordingly.

OTHER SUPPORT:

DINESH M. SHAH, M.D.

ACTIVE

RO1 HD36065 — 1999-2002 — %
NICHD — $745,229
Regulation of Renin and Preeclamptic Hypertension

ACTIVE

[Clapp] — 1999-2003 — %
NICHD
Women's Reproductive Health Research Development Center

ACTIVE

[Maloni] — 1999-2002 — %
NICHD — $126,895
High Risk Pregnancy - Side Effects of Hospital Bed Rest

PENDING

Pending Support

PENDING

Pending Support

% = Percentage of Effort

OTHER SUPPORT:

CLAIRE M. DOERSCHUK, M.D.

ACTIVE

RO1 HL52466-06 [Doerschuk] 08/01/94-07/31/03 %
NIH/NHLBI $170,569
CD18-Dependent and Independent WBC Responses in the Lung

To determine the role of ICAM-1 in leukocyte emigration; the expression and function of cytokines produced by that elicit CD18-dependent or -independent emigration; the role of E-selectin in neutrophil emigration; the role of P-selectin in neutrophil emigration.

ACTIVE

PO1 HL33009-15 [Fredberg] 07/01/95-06/30/00 %
NIH/NHLBI $84,229
Physical Determinants of Lung Parenchymal Function. Project 1: Neutrophil Transit Through the Pulmonary Microvasculature

To understand how neutrophils pass through the pulmonary capillary bed by measuring the dimensions and compliance of capillary segments at physiologically relevant vascular and airway pressures, by modeling the blood flows and pressure gradients across individual capillaries based on these measurements of segment dimensions and compliances, and by measuring the mechanical characteristics of neutrophils using a novel technique.

ACTIVE

5 RO1 HL48160-09 [Doerschuk] 04/01/92-03/31/02 %
NIH/NHLBI $184,015
Neutrophil Sequestration and Emigration in the Lung

To test the hypothesis that biomechanical properties and adhesive properties of neutrophils interact to regulate their response to inflammatory mediators within the bloodstream or the airways.

ACTIVE

RO1 HL48261-07 [Chapman] 01/01/98-12/31/03 %
NIH $5,334
Cystine Proteases Mhc Class II Antigen Presentation

Investigate the role of cathepsis S in antigen presentation and host defense.

ACTIVE

1907 [Doerschuk] 06/01/98-06/01/03 %
Private Support $150,000
The Response of Neutrophils During Inflammatory Lung Disease

To investigate the hypothesis that neutrophil sequestration and emigration in the pulmonary microvasculature occurs through a series of regulated and sequential events involving changes in mechanical and adhesive properties and that these properties are also important in the release of neutrophils from the bone marrow.

Other Support

Name of Individual: Cynthia F. Bearer, M.D., Ph.D.
Active/Pending: Active
Project Number (Principal Investigator): RO1 AA011839
Source: NIH-NIAAA
Title of Project (*and/or Subproject*): Ethanol and L1-mediated Neurite Outgrowth
Dates of Approved/Proposed Project: 1/1/99 – 12/31/04
Annual Direct Costs / Percent Effort: $176,507 / %

The major goals of this project are... The long term objective of this project is to identify the mechanisms underlying ethanol inhibition of L1-mediated neurite outgrowth. This project studies the effect of ethanol on the fibroblast growth factor receptor mediated signaling pathway, and specific L1 phosphorylation events. The hypothesis being evaluated is that ethanol inhibits L1 mediated neurite outgrowth by interfering with L1's downstream signaling cascades.

Overlap (*summarized for each individual*): None

Active/Pending: Active
Project Number (Principal Investigator): 1RO3AA12618
Source: NIH-NIAAA
Title of Project (*and/or Subproject*): Fatty Acid Ethyl Esters in Sheep Meconium
Dates of Approved/Proposed Project: 3/1/00 – 2/28/02
Annual Direct Costs / Percent Effort: $50,000 / %

The major goals of this project are, in a sheep model, 1) to develop a method to normalize fatty acid ethyl esters (FAEE) between subjects, 2) to determine the half-life of FAEE in meconium, and 3) to determine if location within meconium, quantity of FAEE and fatty acid moiety impart information as to dose and timing of dose of in utero ethanol exposure.

Overlap (*summarized for each individual*): None

Active/Pending: Pending
Project Number (Principal Investigator):
Source:
Title of Project (*and/or Subproject*):
Dates of Approved/Proposed Project:
Annual Direct Costs / Percent Effort:

Pending Support

Overlap (*summarized for each individual*): None

% = Percentage of Effort

Active/Pending: Pending

Project Number (Principal Investigator):

Source:

Title of Project (*and/or Subproject*): Pending Support

Dates of Approved/Proposed Project:

Annual Direct Costs / Percent Effort:

Overlap (*summarized for each individual*): None

Active/Pending Pending

Project Number (Principal Investigator):

Source:

Title of Project (*and/or Subproject*): Pending Support

Dates of Approved/Proposed Project:

Annual Direct Costs / Percent Effort:

Overlap (*summarized for each individual*): None

Active/Pending Pending

Project Number (Principal Investigator):

Source:

Title of Project (*and/or Subproject*): Pending Support

Dates of Approved/Proposed Project:

Annual Direct Costs / Percent Effort:

The major goals of this project are....

Overlap (*summarized for each individual*): None

INTRODUCTION

We are enthusiastic and excited by the prospect of continuing our participation in the Cooperative Multicenter Network of Neonatal Intensive Care Units (NICUs). We will demonstrate that we continue to unquestionably meet all the requirements for inclusion as a center. We have the trained personnel, the facilities, data bases and patient population to continue in the Network. Our center has been extremely productive and we have assumed many leadership roles since the inception of the Network. We are committed to collaborative research and the capitation process. Our past record reveals an ability to identify and enroll patients, develop protocols, and collaborate with our colleagues at other Network centers. For this we have the firmest institutional backing and support. This includes commitments of space and resources from the School of Medicine, University Hospitals, the Departments of Pediatrics and Reproductive Biology as well as the Divisions of Neonatology and Maternal Fetal Medicine, and the Director of the Neonatal Follow-up Program. We eagerly anticipate the next cycle for the Network.

A. Requirements for Applicants

1. ACADEMIC PRODUCTIVITY

There is abundant evidence of clinical research productivity by our Center. This derives from Network trials, studies conducted exclusively in our intensive care unit, in addition to other NIH and industry funded collaborative multicenter endeavors.

1a. NICHD Neonatal Research Network Participation. Since the inception of the Network, all the investigators from the Case Western Reserve University, Cleveland site including the Principal Investigators, Nurse Coordinators and Data Managers, have been eager, willing and energetic collaborators. The CWRU Center has contributed significantly to all aspects of the various Network activities. This includes protocol development, patient enrollment, data collection, data analysis, manuscript preparation, and abstract writing in addition to dynamic participation in all Steering Committee and selected Subcommittee meetings. We have participated in and complied with all Network protocols. Our Center has either met or exceeded our projected patient enrollment for all trials. We have been the consummate team players but have, when appropriate, assumed a leadership role for the Network. It is a source of great pride to be a member of the Network which has performed "gold standard" clinical research which is forming the basis for clinical practice throughout the world. (See Appendix I for the full list of Network publications that we have co-authored.)

1ai. Generic Data Base. M. Hack, M.D., the Co-P.I., chaired the original Generic Data Base Subcommittee. She guided the Committee through the onerous task of developing the data base. The first publication derived from the Network data base for the period of 1987-88 has been widely cited (1). The rich data base has been the source of multiple publications and a valuable resource for protocol development (1-5).

Dr. Fanaroff was appointed to the Chair of the Generic Data Base Subcommittee when the Network was expanded in 1991, and he was reappointed to this position in 1999. Under his stewardship the generic data base forms were revised. The birth weight categories were expanded to include birth weights from 401-1500 grams; some data sets were expanded, others deleted, more information was gathered on early deaths, and the CRIB score was integrated into the generic data base. The first from the expanded network highlighted the continued decline in neonatal mortality during the 1991-92 period.

The generic data base has been used to document: a) better outcomes for inborn infants than those transported after delivery (5); b) marked differences in outcome by gender (6); c) the morbidity and mortality associated with low birth weight and multiple gestation; d) factors associated with death within the first 12 hours of life; e) incidence of early onset infection and nosocomial or late onset infection (7,8); f) the impact of antenatal steroids on neonatal outcome (9); and g) the predictive value of the CRIB score in a North American cohort (10).

Since October 1987 we have accurately transmitted the data on 2680 infants with birth weights between 401-1500 grams to the Data Center. This accounts for 8% of 33,424 infants on whom data has been collected by the Network. Our data have been submitted in a timely and accurate manner, and between June 1, 1995 and June 1, 2000 we have added 963 such patients to the data base. The most recent five year period included 484 males, 477 females. The racial distribution included 535 blacks, 408 whites, 8 Hispanics and 10 infants classified as other.

1aii. IVIG Trial. Dr. Fanaroff proposed the first major Network Intervention Trial on the use of intravenous immune globulin (IVIG) to reduce nosocomial infections in very low birthweight infants (VLBW, < 1.5 kg). He chaired the subcommittee for this trial and was first author on the ensuing publication which appeared in the New England Journal of Medicine in April 1994 (11). Our center screened 645 patients, of whom 546 were eligible for the study, and enrolled 355 (65%) of the eligible infants. The trial failed to document a reduction in nosocomial infections with the infusion of IVIG. This contradicted other published studies but, nonetheless, resulted in a change in practice in many neonatal units. An additional publication documented the presenting signs and symptoms of nosocomial infections according to the type of infecting organism and predicted the risk of infection according to birth weight and gestational age (12).

1aiii. Jaundice Prediction. For the prediction of jaundice in term infants by measurement of end expired CO, we were represented on the subcommittee by Dr. Fanaroff. Furthermore, our center confirmed all the carbon monoxide measurements by gas chromatography. We enrolled 89 infants (50 females and 57 white) into the Healthy Term Newborn Trial of whom 11 had hemolytic disorders. Two manuscripts were published (13,14).

1aiv. Dexamethasone Trial. We randomized 43 (12%) of the 371 total study patients in a trial of dexamethasone to reduce chronic lung disease. This represented 57% of those eligible, including 17 females and 28 black infants. Parental refusal or unavailability accounted for 22/31 (71%) of the unsuccessful recruitment. The trial failed to demonstrate benefits from the dexamethasone (15). Indeed dexamethasone increased the risk for bacterial infection (16).

1av. Antenatal Phenobarbital Study. We screened 257 women and randomized 35 subjects, including 16 females and 26 blacks into the Antenatal Phenobarbital Study. The protocol and the infants were diligently followed with cerebral ultrasounds submitted for central reading. The trial, however, was terminated prematurely by the Data Safety and Monitoring Committee, but revealed no benefits to antenatal phenobarbital (17).

1avi. Pulmonary Hypertension Observational Trial. The protocol for this trial was proposed by the Cleveland group. The Steering Committee approved the project and permitted Michele Walsh-Sukys, M.D., a non-member of the Steering Committee, to head the task. Over 400 patients were enrolled including 44 infants from our center. The preliminary results generated three abstracts presented at the 1995 pediatric research meetings (19,20). Originally two manuscripts were submitted for publication but they were condensed into a single manuscript published this year (21).

1avii. Ballard Study. We contributed 75 infants <27 weeks' gestation to the Ballard Study, including gold standard infants where precise dating of the pregnancy was available. Nancy Newman, our Nurse Coordinator, served on the Ballard Subcommittee. The title of the manuscript, "Inaccuracy of the New Ballard Score Before 28 Weeks Gestation", describes the results of the findings (22).

1aviii. Nitric Oxide Trial. In the NINOS trial we randomized 22 of 27 eligible infants including 8 into the congenital diaphragmatic limb of the study. There were 7 white males,4 white females, 5 black males and 5 black females together with 1 Hispanic male and 1 Hispanic female. Eileen Stork, M.D. was our PI for the Nitric Oxide Trial and Debby Cornell, M.S.N. and Ellen Gorjanc, R.N. functioned as study coordinators (23, 24).

1avix. Growth Study. We contributed 189 patients to this study of the longitudinal growth of VLBW hospitalized infants. The manuscript has generated much interest and further efforts to define normal growth patterns for these infants are underway. Dr. Fanaroff served on this committee (25).

1avx. Network Follow-up Study. Dr. Hack has served as a consultant for the development of the Network Follow-up Study. She played a major role in determining when and how the infants should be evaluated, together with the nature of the documentation. She, together with Dr. Deanne Wilson-Costello and Bonnie Siner, R.N., have ensured that our center has been amongst the best follow-up records, and that we comply with the follow-up goals of the study. We have completed follow-up on 94% of infants expected to be followed. Similar follow-up success was achieved in the TIPP Study (see below). Deanne Wilson-Costello, M.D. and Harriet Friedman, M.A., our follow-up psychologist, participated as trainers for follow-up and were authors of the first follow-up manuscript (26).

1avxi. Vitamin A. We enrolled 76 (9.4%) of 807 infants into the Vitamin A Trial. This included 41 females and 47 black infants. Intramuscular administration of 5000 IU of vitamin A three times per week for four weeks reduced biochemical evidence of vitamin A deficiency, and slightly decreased the risk of chronic lung disease in extremely low birth weight infants (18).

1avxii. TIPP. We enrolled 49 infants in this trial to determine whether prophylactic indomethacin would reduce the incidence of neurodevelopmental handicap at age 18 months. Complete follow-up data were obtained on 94% of these infants. The multicenter, multinational trial concluded in April and revealed no differences in the primary outcome between the treatment and the control groups. Indomethacin did significantly reduce the incidence of PDA requiring treatment. The results were presented at the Pediatric Academic Societies (PAS) in May 2000 (27).

1avxiii. SAVE. During the SAVE Trial we enrolled 24 subjects before the trial was halted by the Data Safety and Monitoring Committee. This represents approximately 11% of all the patients entered in the trial. The data were presented at the PAS and has been submitted for publication (21,28).

1avxiv. Glutamine. This trial is in progress. We were amongst the first centers prepared to enroll patients and have, to date, enrolled 41 patients including 25 females and 29 black infants.

1avxv. Body Cooling. Our center has, to date, enrolled one infant into the pilot study of hypothermia to prevent brain injury. Center investigators have been certified and there is IRB approval to embark on the main trial. Dr. Fanaroff is a member of the Study Subcommittee.

1avxvi. Cord Clamping. We are one of four centers participating in a pilot study of the effects of delayed cord clamping on the hematocrit of extremely immature infants. We have enrolled one subject in the week since the study commenced. Dr. Fanaroff helped design the trial with Dr. Oh, and is a member of the Subcommittee.

1avxvi. Surfactant-CPAP. Our center has been the first to start screening patients for enrollment into this study. The first two patients screened did not meet eligibility criteria; one was ventilator dependent and the other not ill enough.

Committees. Dr. Fanaroff served as the Chair on the Publications Subcommittee which reviews all Network manuscripts and abstracts from 1995-2000. He has recently, again, been elected again to chair the Generic Data Base Subcommittee. Dr. Fanaroff has also served a term on the Protocol Review Subcommittee, in addition to the Jaundice Prevention (Tin Protoporphrin) and Skin (Aquaphor) subcommittees. He is currently a member of the Body Cooling Committee, Cord Clamping Subcommittee, as well as the Data Access Subcommittee and the Joint Maternal-Fetal Network-NICHD Neonatal Research Committee.

In summary, the CWRU contributions to the Network operations have been considerable and significant. The investigators have assumed roles of responsibility and leadership of major activities and strongly supported the development and implementation of the other protocols. We chair the Generic Data Base Subcommittee and have chaired the Publications Subcommittee in addition to the Intravenous Immune Globulin and Pulmonary Hypertension Subcommittees. We have had representation on the Necrotizing Enterocolitis, Bilirubin, Surfactant, Pulmonary Hypertension, Nutrition, Cord Clamping, Skin, Body Cooling, Protocol Review and Ballard Subcommittees. We continue to serve on the Data Access Subcommittee and the Joint Maternal-Fetal Network-NICHD Neonatal Research

Committee. We have participated in all Steering Committee deliberations and represented the Network at regional and national research meetings through platform or poster presentations. We have assembled a team who have the experience and qualifications to ensure the quality of the data and manage network functions. We believe that we are an integral part of the Network operation and that our goal, as stated with the initial application to make "the whole greater than the sum of the parts", has been accomplished. The Network has gathered vital data concerning care and outcome of newborn infants. Results of the Network studies have changed practice. The high scientific standards of all the participants have never been compromised. The Steering Committee presents many interesting challenges and we enthusiastically anticipate continued participation in what we believe to be a most worthwhile and rewarding endeavor.

1b. OVERVIEW OF CENTER PARTICIPATION IN NON-NETWORK TRIALS. During the past 15 years priority has been given to Network trials. We have therefore been, to some extent, restricted in collaborating with centers outside of the Network. Nonetheless, the ability of our center to work in a collaborative manner is exemplified by the large number of non-NICHD Neonatal Research Network prospective randomized trials that we have joined in the past five years. These include both NIH and industry-sponsored trials such as the Surfactant Trial for term infants to prevent ECMO, and attempts to predict and prevent hyperbilirubinemia, bacterial sepsis, respiratory syncitial virus infections as well as sudden infant death. The Regional School Age Follow-up Study of infants with birth weights below 750 grams presents evidence of multicenter collaboration within the Northeast Ohio region.

Over the last 30 years we have completed prospective studies as well as chart or data base reviews on a wide range of topics (29-90) (see Appendix II). These include documentation of the effectiveness of CNP in respiratory distress syndrome (29); an evaluation of white cell transfusions for neutropenic neonates (57); a pilot study on the use of intravenous immunoglobulin to prevent nosocomial infections (60); the effect of hypocaloric feedings on gastrointestinal function (48); and an early randomized intervention with high frequency jet ventilation in respiratory distress syndrome (33). Dr. Hook received full cooperation from obstetricians at three institutions in her Caesarean Section study which included over 2000 mother-infant pairs (91). John Kennell, M.D., now assigned to the Behavioral Pediatric Division, has coordinated many trials on the effect of a companion during labor (92).

TABLE 1
Non-NICHD Network Clinical Studies

RESPIRATION
- Constant negative pressure trial (29)
- Nasal CPAP, development (30)
- Nasal CPAP, apnea (31)
- Mechanism whereby CPAP reduces apnea (32)
- High frequency jet ventilation (33-36)
- Transcutaneous monitors (37-41)
- Effect of feeding on ventilation (42)
- Apnea (43)
- Head position (44)
- Surfactant for PPHN (93)
- CHIME
- Premie iNO (94)
- Pulmonary hemorrhage (95)

NUTRITION
- Water balance studies (45)
- Composition of breast milk (46)
- Vitamin D metabolism (47)
- Early feeding (48)

NEONATAL HYPERTENSION (49)

INFECTION
- Clinical studies on Candida (51-53)
- Colonization with fungi (54-55)
- Septic arthritis (56)
- Granulocyte transfusion (57)
- Candida (58)
- Neutropenia (59)
- IVIG (60)
- GBS-impact of guidelines (96)
- Serratia epidemic (97)
- Meningitis (98)
- Ureaplasma (99)

ETHICS & BEHAVIOR (61)
- Doula (92)

DELIVERY ROOM CARE (62-64)

BRONCHOSCOPY (65)

COMPUTER MANAGEMENT (66)

NECROTIZING ENTEROCOLITIS
- Etiology, epidemiology, outcome (67-77)

METABOLISM
- Diabetes in pregnancy (78-81)
- Prediction of Jaundice (100)
- Prevention of jaundice

PHARMACOLOGY
- Clinical trials with antibiotics (83-85)
- IVIG (86)
- GM-CSF prophylaxis (101)
- RSV Immune globulin
- RSV Monoclonal antibody
- Magnesium and CP (102)

MATERNAL INFANT INTERACTIONS (87-90)

NEONATAL FOLLOW-UP (26,98,103-122)

1c. RECENT (FIVE YEAR) PARTICIPATION IN OTHER COLLABORATIVE TRIALS.

1c1. Cardiovascular Effects of Vertically Transmitted HIV. The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted Human Immunodeficiency Virus (HIV) Infection (P^2C^2 HIV) Trial was a multicenter NHL BI-sponsored clinical trial to address cardiopulmonary complications in neonates and infants who are at risk for, or infected with, HIV. The Clinical Coordinating Center for this trial was the Cleveland Clinic Foundation, and Dr. Richard Martin served as investigator on the Coordinating Center. He was involved in the multiple aspects of implementation and execution of this study, including protocol development, data storage, participation in steering committee meetings, and ultimately publication of data as they pertain to neonatal respiratory function (102).

1cii. Surfactant for Term Infants with Pulmonary Hypertension. Sponsor: Ross Laboratories, Columbus, Ohio
As part of a 44 center study we were able to demonstrate that the use of surfactant, particularly in the early phase of respiratory failure, significantly decreases the need for ECMO in the treatment of term newborns with respiratory failure, without increasing the risk of complications. Dr. Eileen Stork was our center PI and Debby Cornell, M.S.N., Nurse Coordinator (93).

1ciii. Granulocyte-macrophage Colony-stimulating Factor (rhu GM-CSF) to Reduce Nosocomial Infections in VLBW Neonates. Sponsor: Immunex, Seattle, Washington
We carried out a randomized placebo-controlled trial in very low birth weight neonates comparing the incidence of nosocomial infections after the prophylactic use of rhu GM-CSF versus placebo in VLBW infants. The absolute neutrophil count and absolute eosinophil count were significantly elevated in the rhu GM-CSF group, however, there was no difference in the incidence of confirmed nosocomial infections (101). We contributed 10 patients to the trial, until there was a conflict with a Network trial to which we steered all eligible patients. Dr. Fanaroff was the center PI, and N. Newman, R.N. Nurse Coordinator. Role: patient recruitment; manuscript preparation.

1civ. Inhaled Nitric Oxide in Premature Neonates with Severe Hypoxemic Respiratory Failure: A Randomized Controlled Trial.
We participated in this trial which demonstrated that low-dose inhaled nitric oxide improved oxygenation but did not improve survival in severely hypoxemic premature neonates. Low-dose nitric oxide in the most critically ill premature neonates did not increase the risk of intracranial hemorrhage, and may decrease risk of chronic lung injury (94). A trial testing this hypothesis has been designed by Drs. Ballard, Martin, Truog and others, and has been funded by NICHD (See Martin extra funding).
We contributed two patients to the trial. Dr. Michele Walsh Sukys, center PI and Debby Cornell, M.S.N., Nurse Coordinator. Role: patient recruitment and data analysis.

1cv. Flumecinol to Prevent Jaundice in Preterm Infants. Sponsor: Farmacon
We contributed 60 patients to this multicenter masked prospective randomized controlled trial of flumecinol to prevent jaundice in preterm infants. Although prior smaller studies had indicated that flumecinol (Xixoryn) prevented jaundice, this was not seen in this trial. There were no adverse side effects noted. Center PI: Dr. Fanaroff; Study Coordinator, S. Bergant, R.N. Role: study design, patient recruitment.

1cvi. The Use of End Tidal Carbon Monoxide (ETCOc) to Predict Jaundice in Term Infants. Sponsor: Natus Medical, San Carlos, California
We contributed over 353 patients of 1370 enrolled in this multicenter, multi-national trial to determine whether ETCOc can predict jaundice in term and near term infants. One hundred and twenty-one (8.8%) of subjects developed significant hyperbilirubinemia. The average ETCOc for the hyperbilirubinemic group was significantly higher (24.7%) than the non-hyperbilirubinemic group ($p < .0001$). Whereas the negative predictive value, i.e., a normal ETCOc and a low serum bilirubin at 30 ± 6 hours after birth was 98.5%, the positive predictive value was not very good (7%). The study demonstrated that some infants with hemolysis do not become jaundiced because they can handle their bilirubin load effectively, whereas other infants with normal rates of bilirubin production do become jaundiced because they have defective elimination of bilirubin. Furthermore, the racial differences in hyperbilirubinemia noted in this

study, which was carried out in Hong Kong, Japan, Israel and the United States, are striking. The data have been presented at the PAS and the manuscript has just been submitted for peer review (100). Center PI: A. Fanaroff, M.D. Role: Study design, instrument validation, writing committee. Study Coordinator: S. Bergant, R.N.

1cvii. End Tidal Carbon Monoxide (ETCOc) to Predict Pregnancy-induced Hypertension (PIH). Sponsor: Natus Medical, San Carlos, California

We have recently concluded the preliminary investigation of measuring ETCOc in pregnant and non-pregnant adults to determine whether this measurement indicates the risk of developing PIH. In collaboration with investigators in Israel and at Stanford University, we have shown that the ETCOc is consistently lower in patients who develop PIH. This preliminary work has just concluded and an abstract has been prepared. Eighty subjects were studied at our center. Center PIs: A. Fanaroff, M.D.; D. Shah, M.D., Reproductive Biology. Study Cordinator: S. Bergant, R.N. Role: study design and patient recruitment.

1cvii. CHIME Study. Sponsor: NICHD. Center PIs: Drs. R. Martin, T. Baird. Study Coordinators: M. Arko, R.N., A. Zadell, R.N. Special Consultant: J. Di Fiore.

In addition to patient recruitment our center played a pivotal role in the development and testing of the monitoring equipment used in the trial.

2. NEONATAL INTENSIVE CARE UNIT STAFFING

The Neonatal Intensive Care Unit at Rainbow Babies & Children's Hospital is a designated Level III (subspecialty) unit. It admits both inborn and out-born infants. The Neonatal Intensive Care Unit (NICU) is staffed by 14 attending neonatologists, all board certified in Neonatal-Perinatal Medicine. There are six neonatal fellows in training. Academically the group is mature and stable with four Professors, and four Associate Professors. The members of the division have extensive experience, both clinical as well as basic research, and have, over the 14 year lifespan of the Network, demonstrated their commitment and willingness to work within the framework of the NICHD Neonatal Research Network.

Avroy A. Fanaroff, M.B., F.R.C.P.E. co-directs the Division of Neonatology and the NICU. After undergraduate and graduate training in South Africa and board certification from the Royal College of Physicians in Edinburgh, he completed a two year neonatal fellowship at Case Western Reserve University (CWRU) in 1971. He was Division Director from1976-1998. He is board certified in Pediatrics and Neonatal-Perinatal Medicine and was re-certified in 1989 and 1996. He is currently a Professor of Pediatrics and Reproductive Biology. He just completed terms on the Pediatric Residency Review Committee, and is completing a five-year term as Chairman of the Organization of Neonatal Training Program Directors. Together with Marshall Klaus, M.D., he is the co-author of Care of the High Risk Neonate, now in its fifth edition, with multiple translations, and with Dr. Richard Martin, Director of the Neonatal Division, edits Neonatal-Perinatal Medicine, a two volume text published by the C.V. Mosby Company currently in its 6th edition. Dr. Fanaroff has been an editor of the Year Book of Neonatal-Perinatal Medicine since 1987. He has been involved in a number of clinical trials and was Principal Investigator of the first randomized intervention study completed by the Network. He has made a major commitment to clinical research and education, and was the recipient of the American Academy of Pediatrics Professional Education Award in 1994 and Neonatal Education Award from the Perinatal Section of the Academy in 1999. As Principal Investigator from CWRU, he has actively participated in the NICHD Network and, in addition to being the PI of the randomized study on the use of IVIG to prevent nosocomial infections, served as Chairman of the Generic Database Subcommittee and Publications Subcommittee. [%] his time is protected for research.

Maureen Hack, M.B., Ch.B., Co-Principal Investigator, received her medical school training in South Africa. After an extended period in Israel, where she trained as a pediatrician, she completed a two-year fellowship in Neonatology at Rainbow Babies & Children's Hospital (RB&C). She returned to Israel for a short period before assuming a faculty position at CWRU. For the past 24 years she has been Director of the High Risk Follow-up Clinic at RB&C Hospital. She is board certified in Pediatrics and Neonatal-Perinatal Medicine. She has published extensively on many aspects on the outcome of low birth weight infants, and is an established investigator with her

[% = Percentage of Effort]

research emphasis on long term growth and development of very low birth weight infants as well as the outcome of the extremely low birth weight infant. She enjoys an international reputation in this field and has continued to receive independent funding from the NIH. She has also served as Co-Principal Investigator for the CWRU participation in the NICHD Neonatal Network, was the first Chairperson of the Generic Database Subcommittee responsible for a number of publications from the Network, and % her time is protected for research.

Richard J. Martin, M.D. is a graduate of the University of Sydney in Australia. After a pediatric residency at the University of Missouri Medical Center in Columbia, Missouri and he completed a neonatal fellowship at RB&C Hospital under the direction of Dr. Marshall Klaus. He has been a Professor of Pediatrics since 1990. He is board certified in Pediatrics and Neonatal-Perinatal Medicine, and in 1998 became Director of the Division of Neonatology. He is an established, well-funded investigator who has completed a number of exquisite physiologic studies on the control of breathing, and is now directing his attention to airway smooth muscle. He is a member of a study section (HED-1), served as a consultant for the NIH on the multicenter HIV cardiovascular study, and has participated in other NIH funded multicentered trials including the HIFI Trial and the CHIME Study, as well as locally sponsored randomized trials, e.g., conventional versus jet ventilation. % his time is protected for research.

Eileen K. Stork, M.D. attended the University of Maryland at College Park, Maryland where she obtained her M.D. After residency and chief residency at RB&C Hospital, Dr. Stork completed a two-year neonatal-perinatal fellowship at the same institution. She is board certified in Pediatrics and Neonatal-Perinatal Medicine. She has attained the rank of Associate Professor of Pediatrics. She is Director of the RB&C Hospital ECMO Program which has now successfully treated over 200 infants. She is also responsible for the Quality Assurance Program at the hospital. Dr. Stork was the center PI on the trial of surfactant to prevent ECMO, and the Network NINOS Trial. % her time is protected for research.

Michele C. Walsh-Sukys, M.D. completed a three year residency at Rainbow Babies & Children's Hospital after obtaining an M.D. at Case Western Reserve University School of Medicine. Following residency she completed a three-year fellowship in Neonatal-Perinatal Medicine. Dr. Walsh-Sukys is board certified in Pediatrics and Neonatal-Perinatal Medicine. She was appointed to the faculty at CWRU in 1988 and served as Vice Chairman for Patient Affairs. She is Co-Director of the ECMO Program and was the Principal Investigator in the Network Observational Study on pulmonary hypertension. Dr. Walsh-Sukys is an Associate Professor of Pediatrics who coordinated the construction of the new children's hospital and, with the aid of a SCIDA fellowship, is completing a Masters degree in Epidemiology with emphasis on health services research. Her protocol on bench marking to improve the outcome of chronic lung disease has been approved by the Steering Committee. % percent of her time is protected for research.

Deanne E. Wilson Costello, M.D. attended Wright State University School of Medicine in Dayton, Ohio, and completed her residency and fellowship at RB&C Hospital. She is board certified in Pediatrics and Neonatal-Perinatal Medicine and an Assistant Professor of Pediatrics. Her main interests are in neurodevelopmental outcome. She has assumed responsibility for the Network follow-up studies and is our center representative on the Follow-up Committee. % percent of her time is protected for research.

The remaining members of the Neonatal Division are listed in the Appendix II along with Division's publications from 1995 to the present.

In summary, we have demonstrated continued productivity within and outside the confines of the Network. We have a faculty with diverse backgrounds and interests who have willingly and actively participated in a number of clinical research protocols. All have expressed a desire and commitment to continue to participate in trials under the auspices of the NICHD Neonatal Research Network.

% = Percentage of Effort

3. PATIENT POPULATION

For the past five years we have admitted in excess of a thousand sick newborns to our neonatal intensive care unit annually (see Tables 2a, 2b).

TABLE 2a

NICU ADMISSIONS • 1995-1999

	1995	1996	1997	1998	1999
Total	1141	1230	1102	1061	1218
Expired	43 [4%]	28 [2%]	31 [3%]	27 [3%]	45 [4%]
Insured	Not available	933	912	857	901
Medicaid	Not available	365	280	277	277
Uninsured	Not available	7	6	5	7

TABLE 2b **NICU ADMISSIONS** • 1995-1999

Transports from Other Centers

Year	Total	Inborn	Level I	Level II	Level III	Total Transports
1995	1141	715		Not available		426 (37%)
1996	1230	965		Not available		265 (22%)
1997	1102	878	131	65	28	224 (20%)
1998	1061	812	166	54	29	249 (23%)
1999	1218	939	162	83	34	279 (23%)

The admissions include inborn patients from the adjacent obstetrical service as well as referrals from within the region and, on occasion, from out of state. Because of the complete range of services (including ECMO and nitric oxide) and highly qualified subspecialists, in addition to the traditional transports from basic and speciality units, the referrals come from other subspecialty units, too (see Table 2b). **Of the admissions to the unit each year, more than 70% are born at our maternity center** and, for the past five years, both the total number of admissions and the proportion of out-born infants have remained fairly constant. The mortality for all admissions has declined slightly, although with a recent trend to the admission of more complex congenital malformations, especially congenital heart disease, this trend may not continue. The improved outlook for infants with birth weights below 1500 grams has been sustained, but their major morbidities, sepsis, chronic lung disease and necrotizing enterocolitis remain a concern (Table 7).

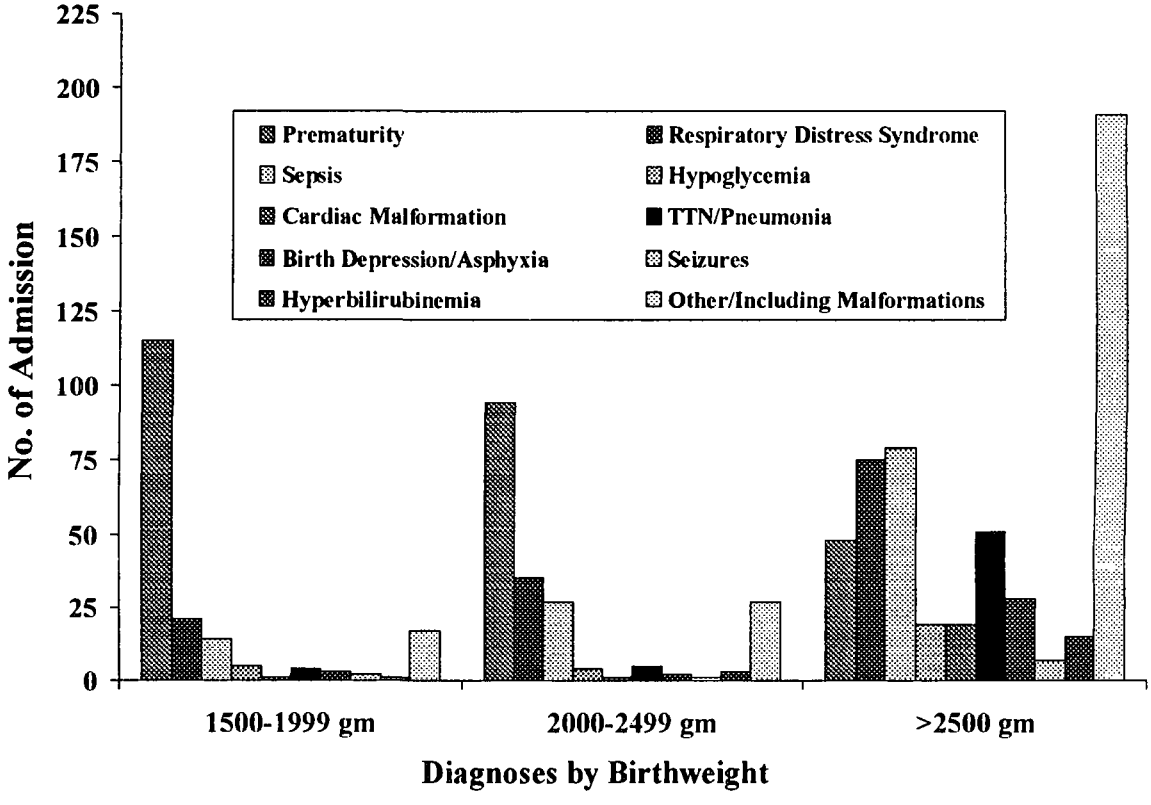
TABLE 3 MEAN LENGTH OF STAY IN DAYS (Survivors)

	1993	1997	1998
BIRTH WEIGHT (grams)			
501-750	139	124	116
751-1000	90	98	87
1001-1250	68	63	57
1251-1500	54	41	46

There has been a slight decline in the length of stay over the past five years (Table 3). Infants below 750 grams who died after admission to the NICU did so at a mean age of 55 days in 1997 (n=8) and a mean of 30 days in 1998 (n=15). Admissions to the NICU include the full range of complex neonatal disorders (see Table 4 below) for the neonatal morbidity of < 1500 gm birth weight infants.

TABLE 4

ADMISSIONS TO NICU OF INFANTS BIRTH WEIGHT > 1.5 KG BY MAJOR ADMISSION DIAGNOSES - MAR 1999-FEB 2000



Over the past five years our Obstetrical Department has demonstrated a sustained level of high activity. Hence, the total number of deliveries has exceeded 4500 for each year from 1995 through 1999 (Table 5). We have collaborated well with the obstetricians who are committed to the Network process and indeed are applying for a Maternal-Fetal Network grant (Table 5).

TABLE 5

UNIVERSITY MACDONALD WOMEN'S HOSPITAL - 1990-1995

	1997	1998	1999
Total Deliveries	4775	4647	4818
Births	4907	4770	4933
Caesarean section	20.3%	20.3%	21.7%
Birth weight			
>2500 gm	84.6%	86.2%	85.6%
1500-2499 gm	9.2%	8.8%	9.5%
<1500 gm	5.2%	5.0%	4.9%
Race			
White	45.6%	46.3%	47.7%
Black	41.4%	41.5%	43.7%
Other (or not noted - Appendix VI)	13%	14.9%	8.6%

The obstetric parameters, which are representative of the inborn population, are detailed in Appendix V. We have a diverse population with a healthy mixture of private and HMO Medicaid patients. The racial breakdown includes approximately almost equal numbers of African-American and white subjects (Table 5, Appendix V). The annual Caesarean section rate is around 20%.

In 1998, of 4648 deliveries, 13% required a primary Caesarean section. There were 120 women with carbohydrate intolerance, 236 (5%) had hypertensive disorders; 183 sets of twins and 27 sets of triplets were

delivered. Two hundred and eighty-four (6%) of deliveries were at 32 weeks or less; and 236 (5%) of infants weighed 1500 grams or less, compared with the national data which indicate that only 1% of deliveries should be in this weight group.

We continue to be among the largest providers of newborn intensive care to indigents in the State of Ohio. We have long prided ourselves on the standard of care offered for all families. Minorities account for approximately 40-45% of deliveries, and more than half of the admissions to the NICU. Minorities have been proportionately represented in the generic data base and various Network trials (Table 6). Between June 1995 and June 2000 we transmitted information on 963 infants for the Morbidity and Mortality Survey, including 468 females. The racial distribution was 535 black, and 408 white, not Hispanic with 18 others. Enrollment in other Network trials by sex and race is tabulated below.

TABLE 6
NETWORK STUDIES ENROLLMENT BY RACE AND GENDER

		FEMALE		MALE		
	TOTAL	BLACK	WHITE	BLACK	WHITE	OTHER
GDB 6/95-6/00	963	288	180	247	228	18
Vitamin A	76	25	15	22	12	2
Glutamine	35	14	9	8	4	
SAVE	24	6	10	5	3	
NINOS	22	5	4	5	7	1
Early iNO	15	2	6	3	4	
PPHN	44	4	10	12	15	3
TIPP	49	16	9	13	11	
Follow-up	301	100	53	83	58	7
Magnesium SO_4	2026	429	432	410	447	289

Our population is typical of tertiary perinatal centers in many large urban cities. Fifty-one percent of the mothers are black, 59% unmarried, and 14% have less than high school education. The table below lists major neonatal morbidities of our VLBW infants for 1998.

TABLE 7
RAINBOW BABIES & CHILDREN'S HOSPITAL SOCIODEMOGRAPHIC, PERINATAL AND BIRTH DATA: 1998
TOTAL VLBW POPULATION (< 1500 gm birth) n = 160
Percent Prevalence

Maternal Demographic Risk Factors		**Infant Birth Data**	
Mean age	27.4	Birth weight (gm, mean)	1007
Married status	49%	501-750	24%
Race (Black)	51%	751-999	23%
Lack of prenatal care	4%	1000-1499	51%
Delivery Room Care		Gestational age by Ballard (wk, mean)	28.7
Antenatal steroids	73%	Gestational age by obstetric parameters (wk, mean)	27.6
Mode of delivery		Apgar < 6 @ 1 min	61%
Vaginal vertex	43%	Apgar < 6 @ 5 min	16%
Vaginal breech	6%	Multiple birth	28%
Caesarean section	51%	Sex (male)	53%
Delivery room resuscitation			
Endotracheal intubation	73%		

TABLE 7 (cont'd) • NEONATAL MORBIDITY

Respiratory Morbidity		**Central Nervous System**	
Respiratory distress syndrome	81%	Seizures	2%
Pneumonia	10%	Ultrasound performed	98%
Pneumothorax	3%	Intraventricular hemorrhage°- Grade I	12%
Apnea treated with xanthenes*	71%	Intraventricular hemorrhage°- Grade II	6%
Oxygen requirement	89%	Intraventricular hemorrhage°- Grade III	5%
Ventilator support	83%	Intraventricular hemorrhage°- Grade IV	2%
Jaundice		Periventricular leukomalacia	4%
Peak bilirubin (mean >10% mg%)*	6%	**Indwelling Catheters**	13%
Patent ductus arteriosus	34%	Umbilical artery catheter	73%
Necrotizing enterocolitis	6%	Umbilical venous catheter	58%
Infection		**Nutrition and Growth**	
Septicemia	31%	Parenteral nutrition (%)*	92%
Meningitis	1%	**Length of Hospital Stay** (mean days)	
Urinary tract infection	14%	Survivors	73

° Infants who had an ultrasound, most severe bleed

* Survivors

4. MATERNAL-FETAL MEDICINE UNIT

The clinical center is located at University Hospitals of Cleveland. The Neonatal Intensive Care Unit in Rainbow Babies & Children's Hospital is in immediate proximity with the Labor and Delivery Unit at University MacDonald Women's Hospital. For each of the past five years we have delivered between 4000 and 5000 patients annually. A substantial number of these patients would be categorized as high risk as the Perinatal Center serves as a resource for consultation and referral from the community obstetricians and the Genetics Center. Women evaluated in the High Risk Pregnancy Clinic receive more detailed evaluation in the obstetric Special Studies facility where a care plan is developed. Some are referred back to their primary physicians, others requiring hospitalization are admitted to the 30 beds available for prepartum hospitalization and ongoing care. Women with antepartum hemorrhage, diabetes of pregnancy, pregnancy-induced hypertension, multiple pregnancies, evidence of severe fetal growth retardation, fetal anomalies, and those with threatened preterm birth, among others, are hospitalized, as necessary, prior to birth. State-of-the-art equipment and modern, newly constructed facilities are available for fetal monitoring and biochemical assessment. The ultrasound equipment plays an integral role in determining fetal anatomy and growth, fetal well-being, the biophysical profile, as well as cardiac function and placental resistance with the use of doppler flow studies.

Our Center for Human Genetics provides state of the art genetic screening and diagnostic testing as well as genetic counseling for families with malformations, inherited metabolic, and other disorders. The staff includes board certified cytogeneticists, medical geneticists, clinical geneticists, molecular geneticists and genetic counselors who assist physicians and patients in Ohio and throughout the country. The Prenatal Screening Laboratory runs in excess of 10,000 patient samples each year, and is one of the country's largest academic prenatal screening laboratories. They pride themselves on reliable and prompt results, usually within 24 hours. The Cytogenetics Laboratory provides high quality chromosome analysis on a variety of specimens including amniocentesis, chorionic villi sampling, peripheral blood and bone marrow. Molecular techniques, such as fluorescence in situ hybridization (FISH) to detect specific abnormalities and better delineate complex karyotypes, are available. The Molecular Diagnostic Laboratory offers direct DNA analysis using PCR methodologies, DNA hybridization, methylation analysis and sequence analysis. The expanded faculty at the Genetics Center, which serves as the largest such facility in the state, serve as consultants for malformed infants diagnosed prior to delivery, and provide counseling for parents of infants with malformations.

Antenatal and delivery care are provided by board certified attending specialists in Maternal-Fetal Medicine under the direction of Dr. Dinesh Shah. They are ably assisted by the perinatal fellows and obstetric residents. Specialized obstetrical, anesthesia and blood bank services are available 24 hours a day. The expanded Labor & Delivery and recovery rooms, which are modern and fully equipped, provide an elegant setting for the family while, at the same

time, offering all the support facilities essential for the perinatal team. Operative deliveries take place in two spacious, fully equipped delivery suites.

The Maternal-Fetal Medicine staff is listed in Appendix III. All the obstetricians are active in clinical research.

Dinesh M. Shah, M.B., B.S., is the Director of Maternal-Fetal Medicine. A graduate of T. National Medical College in India where he received his M.D., he has had extensive training and experience in the United States. He served as a resident in Obstetrics and Gynecology at St. Joseph's Hospital, Northwestern University, Chicago, Illinois from 1977-81, and a fellow in Maternal-Fetal Medicine from 1981-82 at SUNY Upstate Medical Center, Syracuse, New York, as well as a fellow in Maternal-Fetal Medicine, University of South Florida, Tampa, Florida from 1982-83. He was board certified by the American Board of Obstetrics and Gynecology in 1984, and obtained subspecialty certification in Maternal-Fetal Medicine in 1987, with re-certification in 1995. His first faculty appointment was at Vanderbilt University, followed by a position at the University of Texas Health Science Center in San Antonio where he advanced to the rank of Associate Professor in 1993. He was appointed Director of the Maternal-Fetal Division at University Hospitals, University MacDonald Women's Hospital in 1997 and is an Associate Professor of Reproductive Biology at Case Western Reserve University. He has a special interest in, and is a funded investigator in pregnancy-induced hypertension. He also has had extensive experience in managing complex pregnancies including those complicated by fetal malformations and is capable of all the fetal interventions. Dr. Shah has expressed a strong commitment to collaborating with the Neonatal Division in the performance of Network studies and has already been most helpful in the TIPP Trial and the Prediction of PIH Trial as well as establishing the pilot study for delayed cord clamping. Together with Dr. Brian Mercer, he will be submitting an RFA for the Maternal-Fetal Network.

There is a long history of clinical collaboration between the Department of Obstetrics and the Division of Neonatology at CWRU, resulting in excellence in clinical care, maintenance of a data base, and research productivity. There is close collaboration between Neonatology and Obstetrics in the development of care pathways for the management of complicated obstetric patients. This includes those with birth defects, diabetes in pregnancy, hypertension, mothers colonized with Group B *streptococci* and deliveries at the borders of viability. There is a constant interchange of ideas and information between the two divisions. There are also a number of conferences and journal clubs carried out jointly by the two divisions. A Morbidity & Mortality Conference is held monthly in order to discuss all adverse perinatal outcomes. High Risk perinatal conferences have been scheduled and held for the past 20 years, permitting excellent communication between the two clinical staffs (Appendix IV). In addition, because of the large number of patients in whom fetal malformation and other disorders have been diagnosed, a Fetal Board meeting is held monthly. The group attending this comprises obstetricians, geneticists, pediatricians, pediatric cardiologists, pediatric surgeons, pediatric surgical and medical subspecialists, together with genetic counselors. The meetings are held at least on a monthly basis to discuss care plans and outcome for infants with birth defects and other problems which have been identified *in utero*.

There is also a long history of research collaboration between the two divisions. This dates back to a series of studies on diabetes in pregnancy (78-82). Most recently this has translated into a study on vaginal births after previous Caesarean section. This study involved 2000 patients with evidence of both clinical and research collaborative efforts between obstetrics and neonatology as well as the use of the perinatal data base (91). There is a complete and comprehensive data base on all obstetric patients as outlined in Appendix V. These data are collected relating to antepartum, intrapartum, and postpartum care as well as the outcome of the infant. We have used this data base to document the dramatic decrease in the incidence of group B streptococcal infections following the implementation of the guidelines to prevent this disorder. The rate of early onset GBS infection has declined from 2.7/1000 deliveries to 0.4/1000 deliveries.

5. FACILITIES AND CLINICAL CAPABILITIES

A. Facilities

The **Perinatal Center** at University Hospitals has been designated as the Level III (subspecialty) Unit by the State of Ohio. **It comprises the High Risk Pregnancy and Maternity Unit at University MacDonald Women's Hospital and the Neonatal Program at Rainbow Babies &Children's Hospital.** The Neonatal Program includes the 38 bed

NICU, the 45 step-down beds and other infant beds, together with the Follow-up Program, the ECMO Program, and the full array of pediatric, medical, and surgical subspecialists designated above (Appendix III) in addition to the Follow-up, Outreach and Transport programs. Newborns requiring special and/or intensive care are transferred from surrounding counties or, in some instances (mainly ECMO), even other states for specialized care.

The **NICU** comprises 38 intensive care beds. Each bed is equipped with a new (1999) trend monitor capable of monitoring temperature, blood pressure, oxygen saturation pre- and post-ductal, heart rate, and respiration. There are isolettes and radiant warmers and the overhead lighting includes phototherapy units at most of the beds. Each bed has 125 square feet and the unit is divided into modules, the largest being six beds and the smallest as single isolation rooms. Some of the modules have been environmentally modified to reduce sound and light. There is an admission and treatment center with all the capabilities for major surgical procedures. The unit also includes attached clean and dirty utility rooms, a Radiology section, and milk room. There is a conference room together with a Parent Center which includes a lounge, 12 bedrooms, and full bathroom facilities. Adjacent to the Intensive Care Unit is the Respiratory Therapy Laboratory which provides around the clock support and service for the unit. There is a NOVA machine in the NICU for blood analysis using microscopic samples. The NICU, additionally, includes sleeping facilities as well as office space for the Head Nurse, Associate Head Nurses, Social Worker, Residents, and Nurse Practitioners. The laboratory data are available from a number of computer facilities in the Intensive Care Unit and all orders are entered into the many computers in the unit.

The **Convalescent Unit** is located on the fourth floor of the newly constructed, uniquely designed bed tower. It comprises three pods with 11 rooms in each pod. Each room has a crib or isolette with full monitoring facilities and is designed for a single infant (there are a number of rooms for twins or triplets) with sleeping facilities, TV and VCR and a full bathroom for the parents. There is a central monitoring system. The unit is staffed by the Neonatal Division attendings and fellows together with neonatal nurse practitioners and residents. Recently we have started to use this area as a transitional nursery for babies with minor problems and no oxygen requirement.

Laboratory Facilities

(a) Clinical

University Hospitals of Cleveland, which incorporates Rainbow Babies & Children's Hospital, is the major teaching hospital for Case Western Reserve University, and has a complete complement of laboratory facilities which are fully capable of providing prompt service throughout the day and night. This includes the ability to run multiple tests using microtechniques which require the minimal amount of blood withdrawal from newborn infants. Laboratories include Hematology, Chemistry, Endocrinology and Microbiology, with complete facilities for identification and characterization of bacteria, fungi, and viruses. Radioimmunoassays are routinely performed in a number of laboratories including the Special Pediatric Endocrinology and Immunology Laboratory. The Genetic Laboratory processes all amniotic fluid samples, measures the alpha-feto protein, and determines the karyotypes from blood, amniotic fluid, or chorionic villus samples. Molecular techniques, such as fluorescence in situ hybridization (FISH) to detect specific abnormalities and better delineate complex karyotypes, are available. The Molecular Diagnostic Laboratory offers direct DNA analysis using PCR methodologies, DNA hybridization, methylation analysis and sequence analysis.

(b) Research Laboratories

The Neonatal Division has a number of specialized laboratories including two pulmonary laboratories; one for basic science and the other for clinical research; an additional metabolic laboratory, a biochemistry laboratory, drug metabolism laboratory, developmental neurophysiology laboratory, and a pediatric research center.

bi. The Developmental Respiratory Neurobiology Laboratory (2000 sq. ft.) contains a full range of equipment for making cardiorespiratory physiologic measurements in newborn and mature animals (e.g., rodents and piglets). This is complemented by equipment for performing neuroanatomical studies, immunohistochemistry, brightfield, fluorescent and confocal microscopy. We are set up to perform microdialysis to detect neurotransmitter release and perform microinjections. Equipment for molecular biology studies is available for Western and Northern blotting, PCR and RT-PCR. Collaboration with Dr. LaManna allows the recording of intracellular pH and analysis of metabolites in

subregions of the brainstem. Collaboration with Dr. Prabhakar provides access to patch clamp techniques, carotid body recordings, and molecular tools to define expression of early genes.

bii. The Neonatal Pulmonary Research Animal Research Lab (1000 sq ft) is located in the Case Western Reserve University Medical School adjacent to Rainbow Babies and Children's Hospital, and contains a full range of equipment for making cardiorespiratory physiologic measurements. Major relevant equipment available in the Neonatal Pulmonary Research Lab includes: Gould 6-channel strip chart recorder with appropriate amplifiers (integrator, DC and universal), 8-channel Hewlett Packard FM instrumentation tape recorder, Tektronix oscilloscope, force transducers for *in vitro* measurement of airway contractile responses, mouse plethysmograph (Penn Century), Brightfield microscope, video system, and Zidas system for morphometric tissue analysis.

biii. The Drug Metabolism Laboratory (Bearer) is situated in 750 sq. ft. of space in the research area associated with Rainbow Babies & Children's Hospital. The laboratory is fully equipped to perform tissue culture, cellular and molecular biology and analytical chemistry. Equipment includes a fume hood, gas chromatograph, autosampler, integrator and work station, desk-top refrigerated centrifuge, tissue homogenizer, equipment for liquid, paper and thin layer chromatography, pH meter, plate spectrophotometer, Speed-vac, microfuges, four tissue culture incubators, three laminar flow hoods, an upright and an inverted microscope, and gel electrophoresis apparatus. Common equipment in this area includes -70° freezer, ultracentrifuges, analytical balances, sonicator, scintillation and gamma counters, and a dark room with a film developer. Computer-assisted digital microscopy is also available. In addition, the Department of Neurosciences laboratories are fully equipped for advances in cellular, molecular and physiological analyses of neural function. Facilities include: confocal microscopy, electron microscopy, computer-assisted imaging, computers, photography suite and a phosphoimager E707.

biv. The Developmental Neurophysiology Laboratory (Scher) conducts clinical research pertaining to functional brain organization and maturation, and better characterization of brain disorders. Both visual and computer analyses are employed as methodologies in the evaluation of brain function. The present studies are involved in the refinement of a full range of disorders of the brain as defined by our analysis techniques. A combination of video, EEG, and polygraphic data are digitally recorded data sets are used to create algorithms that describe functional brain organization. Collaboration with biomedical engineers have led to the development of both conventional and novel signal processing strategies that more clearly delineate deviations from expected brain patterns. Using these algorithms, together with clinical and epidemiologic data, prenatal and postnatal influences on brain function are being investigated. Better definitions of degrees of brain dysfunction are utilizing video documentation of a full repertoire of clinical signs and behaviors of the preterm and full term neonate that reflect both seizures and non-seizure neurologic activity.

bv. Richard and Marcy Horvitz Pediatric Research Center. The new Richard and Marcy Horvitz Pediatric Research Center was opened in January 2000. It includes 17,800 square feet of research space for basic science, and represents approximately 25% of the total research space available within the Department of Pediatrics. Four research programs are housed in the Pediatric Research Center. These programs include the Polycystic Kidney Disease Center, which is headed by Dr. Ellis D. Avner, who recently was awarded an NIH Center grant to fund this program. The Pediatric Research Center also includes a research program in Pulmonary Inflammation, headed by Dr. Claire M. Doerschuk, which is focused on understanding the acute inflammatory process during pneumonia, acute respiratory distress syndrome, and other lung diseases. Dr. Steven Czinn and Tom Blanchard direct a program in gastroenterology to understand the biology of *Helicobacter* and the development of vaccines against this organism. The fourth program is focused on several aspects of development, and includes a program in cardiovascular development, headed by Dr. Michiko Watanabe, hearing development, and early embryogenesis. All these programs receive substantial NIH support in the form of Center grants, program project grants, and R01s.

c. Office Space

Two rooms in the Biomedical Research Building (Case Western Reserve University School of Medicine) are dedicated as an office for the NICHD Network Coordinator and a data/computer room for data storage, input and analysis. There are two additional offices for the Follow-up Program.

B. CLINICAL CAPABILITIES

We are capable of providing up-to-date care for the most complicated neonatal conditions. Indeed, we are fully equipped and staffed to care for any and all problems encountered in the newborn. **It should be noted that a significant number of our referrals come from surrounding Level III units.** In the NICU the care is rendered by **board certified specialists** and **subspecialists** who supervise trainees. The **Fellowship Program** in Neonatal-Perinatal Medicine at Rainbow Babies & Children's Hospital has been operative since 1967. There are presently six fellows in training including two third year, two second year, and two first year fellows. Their clinical experience is divided among the 38 bed intensive care unit at Rainbow Babies & Children's Hospital, the Step-down Unit and Follow-up Clinic at the same institution as well as the delivery room. In addition, they attend high risk deliveries and serve as consultants at four community hospitals encompassing approximately 3500 deliveries.

The **nursing staff patterns** in the Neonatal Intensive Care Unit, as well as the Step-down Unit and Normal Newborn Nurseries, are indicated in Appendix VI. The nurse-to-patient ratio is determined by the acuity of the patient, as the patients with severest illness will have a ratio of 1:1 or, in the case of patients on extracorporeal membrane oxygenation (ECMO), there will be a primary nurse and ECMO Specialist at bedside around the clock. For patients with lesser acuity the common ratio is two patients per nurse in the intensive care unit. Only on occasion will there be a ratio of one nurse to three patients. A primary nurse is designated for each patient and they facilitate interactions with the family. There are very strong quality assurance programs in the nursery carried out at three different levels, namely physicians, nurses and respiratory therapists. In addition to the physicians, nurses, and nurse practitioners, there are dedicated neonatal social workers. A member of the pharmacy staff is also assigned to the NICU and at least three respiratory therapists are assigned for each shift. Both Pharmacy and Respiratory Therapy have willingly and effectively participated in Network trials, and have made certain that the masking of the therapy is not compromised.

The **Nurse Practitioner Program** is well established and, as of July 2000, there will be 16 full time nurse practitioners. The **Resident Training Program** is extremely strong, and with the help of the residents we are able to provide excellent patient care.

Rainbow Babies & Children's Hospital has a full array of **pediatric subspecialists** (Appendix III). They are able to provide prompt consultation as well as ongoing care for infants either delivered at our institution or transferred in from the surrounding five counties which is the main referral area for Rainbow Babies & Children's Hospital. The core of subspecialists include **medical** as well as **pediatric surgical subspecialists**. There are, furthermore, many specialty clinics which include, but are not limited to, Cardiac Electrocardiography, Familial Hyperlipidemia, Electrocardiography Laboratory, Pacemaker Clinic, Center for Disorders of Growth and Development, Center for Inherited Disorders of Energy, Metabolism, Behavioral and Developmental Clinic, Child Protection Program, a special study group on perinatal effects of cocaine, Hemophilia Treatment Center, Sickle Cell Anemia Center, Sleep Study Laboratory, Center for Drug Research, Poison Control Center, Center for Medical Information and Statistics, Asthma and Cystic Fibrosis Center, Pulmonary Function Laboratory, School Age and Premature Follow-up Programs, and Learning Disability Center. There are specialized clinics for infants with birth defects and myelodysplasia as well as cranial facial disorders. A partial list of research laboratories include Airway Epithelium Transport, Body Surface Potential Mapping, Cystic Fibrosis Cell Biology, Embryology, Epithelial Ion Transport, Immunology, Intracellular Regulation, Lung Inflammation, Mucil Biochemistry Laboratory, and Neonatal Metabolic Lab.

The institutional Pharmacy has proven to be both willing and able to participate in multicenter trials. They have provided the randomization codes, parenteral nutrition, and drugs for infants participating in the intravenous immunoglobulin, phenobarbital, dexamethasone, vitamin A and glutamine studies. The record keeping has been beyond reproach, and they are anticipating a continued relationship with the Neonatal Division in future clinical trials. Furthermore, the Center for Drug Research in the Department of Pediatrics at Case Western Reserve University, under the direction of Jeffrey L. Blumer, Ph.D., M.D., has a long history and experience of developing and conducting clinical trials of drugs in infants and children. They are a member of the Network of Pediatric Pharmacology Research Units funded by the National Institute of Child Health and Development. They have an expressed interest to collaborate with the Neonatal Network in appropriate trials (see letter of support).

The Respiratory Therapy Department at Rainbow Babies & Children's Hospital has a long tradition of collaborating in clinical research. The Respiratory Therapy Department at Rainbow Babies & Children's Hospital has assumed leadership in pediatric respiratory education, exemplified by the initial pediatric respiratory therapy book edited by Lowe, Doershuk and Stern and published by Yearbook Medical Publishers, and Neonatal Respiratory Care, 2nd edition, Carlo WA, Chatburn RL (eds), Yearbook Medical Publishers. We are indeed proud of the capability and performance of the Respiratory Therapy Department at Rainbow Babies & Children's Hospital. The Department of Pediatrics Respiratory Care has 20 respiratory care practitioners who rotate through the NICU. There are 30 dedicated neonatal ventilators. They assisted us greatly in initial controlled trials of CPAP in respiratory distress. Robert L. Chatburn, RRT, Director of Respiratory Therapy, designed and built a jet ventilator, which was used in a randomized clinical trial carried out by Carlo (33) in a comparison of jet ventilation with conventional ventilation for infants with respiratory distress syndrome. The respiratory therapists have been trained to deliver surfactant, and willingly and eagerly participated in the head-to-head surfactant trial as well as the Surfactant Trial for the prevention of ECMO. They are prepared to participate in the Surfactant/CPAP Trial which has just been launched. They have been responsible for administering drug or placebo, and in maintaining the masking. They also assisted us in the Nitric Oxide Trial with responsibility for delivery of the appropriate gas with clinicians unaware of which agent is being administered to the infant.

The Radiology Department has an extremely competent staff, wide range of equipment and the necessary expertise to interpret the films. In addition to the standard X-ray techniques, there are an adequate number of the latest generation of ultrasound machines which incorporate color flow doppler for both antenatal and post delivery use. There are also the latest models of CT scanners, PET scanners, and MRI scanners available. The Radiology Department has been very cooperative with performing our required studies in a timely manner.

NICU Follow-up Program

The NICU Follow-up Program under the directorship of Dr. Maureen Hack has, since 1975, followed all < 1.5 kg birth weight infants until 18-20 months corrected age. This program is ongoing and data pertaining to the children's outcomes have, over the years, become the subject of many publications. School age follow-up studies of selected very low birth weight (VLBW) cohorts have also been periodically studied (see below). Infants with chronic lung disease discharged home on oxygen are followed clinically in collaboration with the private pediatricians of the patients within the context of the NICU Follow-up Program. Furthermore, other selected larger birth weight infants are also followed. Since the initiation of our ECMO Program in 1987, these infants have been followed in a separate ECMO Follow-up Program directed by Dr. Michele Walsh-Sukys (see below).

The infants are enrolled in the Very Low Birth Weight Follow-up Program prior to discharge from the hospital, and examined in the Follow-up Clinic at 40 weeks corrected age (expected age of delivery), 4, 8 and 18-20 months corrected age. Approximately 50% of the children receive pediatric care from private pediatricians in the community, and 50% from the Ambulatory Pediatric Clinic at Rainbow Babies & Children's Hospital. The Neonatal Clinic is held twice weekly. The program provides clinical consultative support to the caretaking pediatrician, and provides the basis for our clinical research program. At each visit weight, height, head circumference and development are assessed. At 40 weeks, 4 and 8 months corrected age, the Amiel-Tison Neurologic Assessment is performed, and at 18-20 months a standard pediatric neurologic examination. The Bayley Scales of Infant Development are performed on all infants at 8 and 18-20 months corrected age. The BSID-II (the revised Bayley Scales of Infant Development) was introduced in 1991. Children born since 1992 have been tested with these revised scales. The forms for data collection are included in Appendix VII. Studies of children at older ages are undertaken only for funded research protocols (NIH RO1 HD 34177-04, NIH RO1 HD 26554-05, NRO 1894-06A1).

A summary of outcomes at 20 months corrected age for < 1000 gm birth weight children born during the years 1992 through 1995 follows. For a complete description of these outcomes, their perinatal correlates and predictors, see the Appendix VIII.

In this '92-95' cohort 95% of infants discharged home were followed to 20 months corrected age, and 92% had complete Bayley Developmental Assessments. The rate of overall neurosensory impairment including spastic diplegia,

quadriplegia, hypotonia/hypertonia and shunt dependent hydrocephalus was 20% at 20 months. The rate of cerebral palsy (spastic diplegia, hemiplegia and quadriplegia) was 15%. The rate of neurodevelopmental impairment, including Bayley Mental Developmental Quotient < 80 and/or neurosensory impairment was 48%.

We are currently examining outcomes for the years 1996-1997. Preliminary examination reveals that they do not differ from the 1992-1995 outcomes presented above.

Throughout the years, all infants born at < 1500 gm birth weight have been studied, however, since 1992 emphasis has been on getting an excellent return rate on < 1000 gm birth weight infants with less emphasis on the 1000-1500 gm birth weight infants. Our follow-up rates have consistently been the best of the NICHD Neonatal Network follow-up centers, and in excess of 90%.

Professional Staff - The professional staff of the Follow-up Program includes Maureen Hack, M.D., Director of the High Risk Clinic; Deanne Wilson-Costello, M.D., Assistant Director; a clinic coordinator (% FTE) who assists in the recruitment, scheduling and tracking of patients as well as data compilation; a developmental specialist, Mrs. Harriet Friedman, M.A., Clinical Developmental Psychologist (% FTE), who performs the Bayley Scales of Infant Development and counsels parents; a part-time clinic secretary (30% FTE); a nurse researcher from the funded programs who assists in data collection specifically related to their program. For example, Mrs. Bonnie Siner, R.N. administers the questionnaires related to the NICHD Follow-up Program and assists in examination of the children. Neonatal fellows attend Follow-up Clinic during their clinical service rotation. Children with oxygen dependence are followed by the attending neonatologists, Drs. Jill Baley and Deanne Wilson-Costello.

The clinic office space includes two 12x12 ft. rooms housing the support staff. We furthermore utilize four rooms of the Ambulatory Clinic twice weekly for examination of the children, as well as three rooms of the Clinical Research Center including a testing room for performance of the Bayley Scales of Infant Development. This space will also be available for examination of other selected cohorts of school age children (RO1 HD 34177-04). There is also space available in the adjacent building for NIH-funded continuation of the < 750 gm birth weight School Age Follow-up Program (RO1 HD 26554-05A1) (see below).

Affiliated Follow-up Programs

1. School-age Follow-up Program of < 750 gm Birth Weight Infants, under the directorship of H. Gerry Taylor, Ph.D. and Maureen Hack, M.D., is funded by NIH RO1 HD 26554-05. This program was initially funded from 1990-1992 and from 1994-1999. The regional cohort of 197 children includes 68 < 750 gm, 67 750-1499 gm, and 62 term born matched control children. These children were initially studied at age 6-8 years on measures of growth and development. The funding from 1994 to 1999 allowed for annual assessment of the children for four years to measure possible changes in health, growth and developmental status. Funding for an adolescent continuation of this study is pending.

2. ECMO Follow-up, is under the directorship of Dr. Michele Walsh-Sukys. This program was initially established for infants with severe pulmonary hypertension (PPHN) including those treated with ECMO. Data have been utilized in publications, and are used to track regional outcomes for these infants. This clinic continues to follow all neonates with PPHN and is involved in the ECMO Follow-up Study and the current NICHD Neonatal Network Nitric Oxide Study.

3. BPD Research Follow-up, under the directorship of L. Singer, Ph.D., and funded by NIH HL 38193 and MCH 2-MCJ-390592, is examining the outcomes of very low birth weight children born in 1989 to 1991 and their relationship to growth and development. These children were initially followed to three years of age and are currently being followed at school age.

% = Percentage of Effort

4. Assessment of Biological and Social Risk in Preterm Infants (NR01894-061, PI: D. Holditch Davis) and a Multicenter Study of Sleep and Outcomes in High Risk Infants, PI: M. Scher (NS 34508-02). These two studies are examining the predictive validity of neonatal EEG on late outcomes. VLBW children in these studies also participate in our VLBW Study and some term born children participate in the ECMO and PFC Follow-up Studies.

5. Outcomes of VLBW Infants Who Receive Breastmilk. Dr. Lydia Furman, in collaboration with Dr. Hack, is performing an observational study of the neonatal and 20-month outcomes of VLBW infants born 1997-1999 who received breastmilk. She is also examining the correlates of breastmilk feeding in this population. This study is funded by research funds from the Department of Pediatrics.

6. Young Adult Outcomes of VLBW Children Born 1977-1979. Subject intake from this NICHD-funded study (RO1 HD 34177-04) has recently been completed and the data are currently being analyzed.

7. School Age Outcomes of < 1000 gm Birth Weight Children (RO1 HD 39756-01, pending). A grant proposal to examine health and functional outcomes of < 1000 gm birth weight children born 1992-1995 at 8 years of age is pending.

STRENGTHS

The strength of our center lies in our experienced Network team who has the ability to integrate and harmonize Network functions with our nursery personnel and their daily patient care routines. We have participated in a variety of randomized trials, simple and complex where we have demonstrated the ability to rapidly gain the approval of our colleagues for the trial. We have also been amongst the first centers to have the study reviewed and approved by our Institutional Review Board, complete Network certification procedures and commence patient enrollment. Furthermore, we are dedicated to fostering good relationships with our colleagues and co-investigators, a goal facilitated by the personalities of our Network representatives. We have a critical cohort of committed Network personnel who have, for almost 15 years, demonstrated the ability to involve other faculty so that the multicenter study goals can be achieved, while, at the same time, the many resources of the institution are utilized and the quality of patient care is enhanced. Indeed, the search for evidence-based practice blends the goals of the clinicians and investigators. Our professional staff has become accustomed to the clinical trials and have assumed pride of ownership.

Our medical center combines a number of desirable attributes such as the close proximity of the clinical areas, the medical school and the university. Furthermore, a children's hospital within a large university hospital complex ensures the availability of all the subspecialists, laboratories and scanning facilities which may not be present in a stand alone children's hospital. We are also able to take advantage of the proximity of the basic science departments for molecular biologic techniques and biomedical engineering. There are ample laboratories for basic science as well as clinical research.

There are a number of unique programs and facilities such as the Genetics Center, the Center for Drug Research, the Center for Medical Informatics and Statistics, in addition to the Center for Inherited Disorders of Energy Metabolism (CIDEM), which are readily available for Network research activities. The Clinical Pharmacology Program is a member of the NICHD Network of Pediatric Pharmacology Research units.

It has not been necessary to modify clinical services to support clinical research.

6. PERINATAL DATA SYSTEM

We have several interrelated and overlapping systems which retrieve data on elements of neonatal intensive care. These include:

(a) A comprehensive computerized data bank and collection system pertaining to all very low birth weight infants (see below and Appendix VIIb).

(b) The modified Hobel Perinatal (antepartum, intrapartum and neonatal) Assessment System for all infants delivered at the perinatal center. The inborn perinatal data system is computerized (Appendix Va).
(c) A computerized data bank for all admissions to the NICU.

a. Very Low Birthweight Infants

Our major interest and research focus has been on the very low birth weight infant. In 1977 a data bank of risk factors was established by Dr. Hack to prospectively monitor the effects of the many interventions and treatments currently in use in the NICU. This data bank, initially funded as part of the Regional Perinatal Network, is ongoing and constitutes the initial data input of the Very Low Birth Weight High Risk Follow-up Program. Special forms modified from Hobel's system which document social, antenatal and perinatal risk factors, were updated in 1989 and 1999 to conform to current modes of treatment and changing neonatal morbidity (Appendix VIIa). Forms are used to prospectively record the birth data, neonatal intensive care events, disease processes, nutritional and metabolic disturbances as well as all treatment modalities. Autopsy results and cause of death are documented separately. These forms were the basis for the initial generic database of the NICHD Multicenter Network. The follow-up component of the data system includes an assessment of growth and development at 40 weeks (expected date of delivery), 4, 8 months corrected age and then at two years of age. The selected subgroup of children born 1977-1979 and 1982-1986 have also been assessed as they enter school and again as teenagers.

All the above data are presently stored as system files using SPSS PC+. At birth, on admission to the neonatal intensive care unit, each infant is assigned a study identification number, which is used to connect subsequent waves of data. Ms. Nori Mercuri-Minich, who was initially a data programmer, has assumed responsibility for the management of this database. Her familiarity with this database, which was merged and expanded, has permitted ongoing evaluation of various cohorts (see Follow-up publications). Ms. Minich has a strong background in the multivariate techniques needed for the model testing including OLS, logistic and multinomial regression, and longitudinal modeling using path analytic techniques and structural equation modeling. The cohort of VLBW births from 1975-1999 inclusive, with complete antenatal, intrapartum and neonatal data, thus form the nucleus of the program and have permitted many studies (see reference 103-122).

The data have been used to document:

i. **Annual Mortality and Morbidity Statistics** (Appendix VIIc).

Of note is the increase in mortality during 1994 for <750 gm birthweight infants. In retrospect, this may have been attributed in part to benzyl alcohol toxicity. Subsequent to the FDA warning in May 1982, the use of benzyl alcohol in the flush solutions for arterial catheters was discontinued in the nursery. After that time there was a dramatic decrease in mortality. A change in vendors resulted in the inadvertent reintroduction of a flush solution with benzyl alcohol.

ii. **Demographic and Perinatal Data** (Table 7).

iii. **Etiology and Neonatal Outcomes of Term Small for Gestational Age Infants**

We recently utilized the perinatal data base to determine that 372 (9.1%) of 4879 infants delivered at University MacDonald Women's Hospital in 1997 were small for dates according to the national birth weight standards. The SGA infants (mean birth weight 2609 ± 206 gm) were compared to appropriate for gestational age controls (mean birth weight 3310 ± 301 gm), matched for gestational age, gender and race. Despite higher rates of multiple birth, maternal hypertension and smoking, the neonatal adverse outcomes of SGA infants born at term gestation were minimal and confined to severe growth failure. Only two infants died, both with severe malformations. We postulated that current perinatal and neonatal practice prevents the previously described neonatal morbidity in growth retarded term infants.

iv. **Implementation of the Guidelines for Prevention of Early Onset Neonatal Group B Streptococcal (GBS) Sepsis.**

We have used the data base to monitor the effects of the implementation of the guidelines for preventing early onset GBS sepsis. We have documented an increase in the number of women screened, the number of women colonized and the number of women treated intrapartum with antibiotics. This has translated into fewer invasive

procedures on the neonates (fewer blood cultures and fewer spinal taps), as well as fewer infants receiving antibiotics. There has also been a significant decline in the incidence of early onset GBS sepsis (Appendix Vd). This suggests that the guidelines have been effective both from a clinical and economic stand point (96).

We have also monitored the incidence of late onset sepsis, documenting no significant change, nor have we observed an increase in infections with antibiotic resistant organisms.

v. Of special interest has been our study of the outcomes of **<750 gm birthweight infants.**
Dr. Hack has continued to pay special attention to this cohort and has reported on the short and long term outcomes including their school performance. There continues to be significant morbidity amongst these infants. (62,63,121).

vi. The close monitoring of nosocomial infections is illustrated in Appendix IX. Despite all our efforts the rates of nosocomial infection remain high in the smallest, least mature infants.

7. RESEARCH NURSE STAFFING

For the past 20 years the Neonatal Division has been privileged to have the assistance of extremely competent, diligent, highly motivated, skilled, full time, dedicated research nurses. They have all had extensive experience in the NICU and most have been certified in ECMO. They were hired initially utilizing departmental and divisional resources, and are currently funded through research grants, hospital, and department funds. The research nurses have been responsible for patient recruitment, enrollment, data gathering and preparation, in addition to data analysis and protocol development. They have been invaluable in our interface with the Institutional Review Boards, notably by assuming a major role in the development of the informed consent documents. Their skills and knowledge have resulted in them being extremely successful in recruiting and retaining patients for a wide variety of study protocols.

The Research Nurse Program was expanded through our initial participation in the NIH sponsored High Frequency Multicenter Trial and our subsequent admission to the NICHD Research Network. We have an experienced cohesive team who is available around the clock to enroll patients and perform the duties necessary to ensure adherence to the various protocols. The group has worked well with their peers at other Network centers and take great pride in their accomplishments. In addition to successfully recruiting patients into all the Network protocols, their record keeping has been superb. They have ensured accurate and timely transmission of data to the Coordinating Center. The nurses have been included as authors on a number of publications because of their active involvements in the various phases of study design and implementation.

Nancy Newman, R.N. has served as the Nurse Coordinator of the NICHD Network since the inception of the Network. Because of her extensive experience she has been a valuable resource to other Network coordinators as well as Principal Investigators and the NICHD staff. Nancy Newman has, again, been identified as our center coordinating research nurse, a task she eagerly looks forward to. She is and will be ably assisted by Bonnie Siner, a former neonatal intensive care nurse who has devoted the past 20 years to research-related activities. Bonnie Siner has received extensive training in respiratory physiology and also neonatal follow-up. She now assists Drs. Maureen Hack and Deanne Wilson with the follow-up component of Network and other studies. Sue Bergant, R.N. joined our research nursing team in 1994 and has been a valuable addition. She has assisted with ongoing Network studies and been primarily responsible for studies related to bilirubin. This has included the use of flumecinol to prevent jaundice in preterm infants; the validation of the end tidal carbon monoxide (ETCOc) instrument to predict jaundice, as well as the validation of the transcutaneous Bilicheck instrument to measure jaundice.

Marino Arko, R.N and Arlene Zadell, R.N. are two additional research nurses who have been responsible for the control of breathing studies and the CHIME Study. They are talented individuals with excellent communication skills who will coordinate the inhaled nitric oxide to prevent chronic lung disease study which has recently been funded. R. Martin, M.D. is our center PI.

The Neonatal Network research nurses are complemented by other research nurses and associates within the Neonatal Division. Two additional nurses, Deborah Cornell, M.S.N. and Ellen Gorjanc, R.N. who coordinate the ECMO Program, have been responsible for protocols relating to pulmonary hypertension. Hence, they have been of immense value in the Network Observational Study on pulmonary hypertension as well as the Survanta Trial to prevent ECMO, and the Network Nitric Oxide Trials.

Juliann DiFiore, B.S.E.E., is a biomedical engineer and research associate within the Neonatal Division who played a major role in the CHIME Study and the pulmonary function studies related to nitric oxide in the prevention of chronic lung disease.

The Head Nurse in the Neonatal Intensive Care Unit, Ann Reitenbach, together with all the staff nurses and neonatal nurse practitioners, are committed to clinical research and the concept of multi centered randomized trials. A NICU nurse is designated as the trials coordinator. Nancy Newman is responsible for in-servicing the NICU nurses on the various study protocols so that they have enthusiastically cooperated in the conduct of Network trials. This has facilitated patient recruitment.

The research nurses have participated in a large number of clinical trials (Table 1). These include studies on nutrition, control of ventilation, mechanical ventilation, cardiovascular disorders, neurologic problems, metabolic disorders, labor and delivery, and infections. Our Network Coordinator, Nancy Newman and Data Manager, Janet Sterl, have extensive experience and are well qualified to ensure the quality of data from our center and to manage Network activities in close collaboration with the Principal Investigators.

In summary, we have a cohesive, experienced and talented group of research nurses. They have demonstrated their ability to recruit and retain patients for many collaborative studies. Furthermore, through their efforts we have consistently been one of the first Network centers with IRB approval, and personnel certified and ready to enroll patients for the Network trials. Nancy Newman, our Research Coordinator, has served on the Protocol Committee, and was a key person in the modification of the generic data base form. She has consistently been called upon to determine the nursing time involved in studies so that the appropriate capitation can be calculated. She has been a leader amongst the coordinators whose practical advice has assisted them in implementing trials at their centers.

8. Proposed Concept Protocol: A Randomized Trial of Continuous Positive Airway Pressure to Prevent Bronchopulmonary Dysplasia in Extremely Low Birth Weight Neonates

8a. Hypothesis and Specific Aims.

Survivors of premature birth have a high incidence of chronic lung disease termed bronchopulmonary dysplasia (BPD) which leads to long term health impairments. In the United States premature infants with respiratory distress syndrome are generally treated with mechanical ventilation. Recent work in the United States and Europe suggests that avoidance of mechanical ventilation may reduce the incidence of BPD. Thus, we propose a randomized controlled trial in neonates < 1250 grams birthweight of early nasal continuous positive airway pressure (CPAP) versus early mechanical ventilation to reduce the incidence of BPD.

Hypothesis: Neonates with birthweight 601- 1250 grams randomized to nasal CPAP at < 6 hours of age will have less bronchopulmonary dysplasia than those treated with mechanical ventilation.

Specific Aims:

1. To determine the incidence of BPD at 36 weeks' gestation in neonates treated with nCPAP or mechanical ventilation.
2. To assess the safety of the primary use of nCPAP in high-risk neonates as measured by the frequency of apnea, intraventricular hemorrhage or periventricular leukomalacia, and patent ductus arteriosus.
3. To compare resource use between those receiving nCPAP or mechanical ventilation (doses of surfactant received, days of mechanical ventilation, days of nCPAP, days of oxygen use, duration of hospital stay, discharge home with oxygen).

8b. Background and Significance.

Bronchopulmonary dysplasia is a multifactorial disease that occurs when immature lung parenchyma is injured and incompletely repaired. Contributing injurious factors include inflammation resulting from antenatal and/or postnatal infection, oxygen toxicity and volutrauma, and lung edema resulting from patent ductus arteriosus. Repair factors include overall nutritional status and the sufficiency of vitamin A stores. The interplay and relative importance of these various factors is incompletely understood (123,124,18). Bronchopulmonary dysplasia (BPD) is a significant health burden. Sequelae include frequent hospital readmissions for reactive airway disease, long term abnormalities in pulmonary function, and an increased rate of adverse neurodevelopmental outcomes (125,126,127,26). According to the NICHD Neonatal Research Network, 83% of very low birth weight neonates (VLBW, < 1500 gm) survive, and 19% of the 2853 VLBW neonates born in 1994 developed BPD (4). The incidence of BPD, defined as oxygen use at 36 weeks corrected age, varies inversely with gestational age. Ninety-five percent of all neonates with BPD at 36 weeks corrected age are < 1250 gm at birth, thus these infants are the at risk cohort.

Recent trials to prevent BPD have focused on interventions to decrease inflammation through the use of corticosteroids, or treatment with vitamin A (128,129,15,18). Initial enthusiasm for corticosteroid use has waned as increased adverse events and long-term neurodevelopmental sequelae have been revealed (130,125,126,28). Vitamin A has proven an effective intervention with an absolute reduction of BPD of 7% (18). Other interventions are needed to further reduce this important morbidity.

Several studies have suggested that volutrauma resulting from mechanical ventilation plays a pivotal role in the development of bronchopulmonary dysplasia. Avery was the first to suggest that variations in the rate of BPD might be due to differing practice patterns between neonatal intensive care units (NICU) (131). Avery compared the rates of BPD between eight NICUs and found that the center with the least BPD, subsequently identified as Columbia Babies and Children's Hospital, used early continuous positive airway pressure (CPAP) as the preferred method of respiratory support with a more limited use of mechanical ventilation. Recently, VanMarter and colleagues extended these observations through an in depth comparison of treatment practices between two New England NICUs and Columbia Babies and Children's Hospital (132). Again, Columbia was shown to have a low rate of BPD (4% versus 22%). In multivariate analyses adjusting for birthweight and severity of illness, the majority of the variation in BPD was explained by practices of initiating ventilation including the early and routine use of CPAP. Thus, observational evidence supports the premise that early use of CPAP could avoid mechanical ventilation and reduces the incidence of BPD.

Neonatologists in the United States may not have utilized CPAP because of concern for apnea in tiny premature infants. In randomized controlled trials conducted by Verder and colleagues of the Danish-Swedish Multicenter Study Group neonates < 30 weeks' gestation were randomized to surfactant and early CPAP versus ventilation. The use of mechanical ventilation was decreased from 83% to 33% (133). A second study by the same investigators showed similar results with an improved outcome in the group receiving treatment within six hours of birth (134). In each study, approximately 40% of those babies assigned to CPAP developed apnea and required intubation for this indication. Thus apnea must be considered, however, in these trials the use of aminophylline or caffeine, potential treatments for apnea, were not standardized. An additional concern preventing neonatologists' routine use of nasal CPAP may be concern that the nasal prongs do not fit in the nares of the tiniest infants. This concern may be overcome by selection of the neonates studied.

Thus, we propose a randomized controlled trial in neonates < 1250 grams birthweight of early nasal CPAP versus early mechanical ventilation to reduce the incidence of BPD.

8c. Design and Methods.

Type: Multicenter randomized controlled trial.

Inclusion Criteria:
1. Inborn neonates 601-1250 gm birthweight.
2. FiO_2 < 80% to maintain oxygen saturation 90-96%.

Exclusion Criteria:
1. Neonates with major congenital anomalies.
2. Neonates with a 5 minute Apgar < 3.

Intervention: Nasal CPAP versus mechanical ventilation.

Management Protocols: Surfactant administration will be standardized between the two groups with surfactant administered to any patient requiring >30% oxygen to maintain a PaO_2 50-60 torr. Infants in the nCPAP group will be promptly extubated. Treatment of apnea will be aggressive and standardized between the two groups with early use of caffeine in any patient with apnea. Other management measures will be left to the discretion of the treating attending physician.

Consent: Informed written consent from the neonate's parent will be obtained either antenatally or within six hours of birth to enable early randomization.

Randomization Schema: Centralized randomization with stratification into 601- 750 gm, and 751-1000gm , 1001 to 1250 grams treatment strata; also stratified by center.

Masking: Unmasked intervention.

Primary Outcome: Survival free of bronchopulmonary dysplasia at 36 weeks corrected age as defined by a standardized physiologic test which designates cases of bronchopulmonary dysplasia utilizing oxygen saturation.

Primary Endpoint Definition: One of the confounders in any randomized trial that uses bronchopulmonary dysplasia as an outcome is the lack of a standardized definition of BPD. BPD has traditionally been defined by oxygen administration at 36 weeks corrected age. An assumption has been made that all physicians prescribe oxygen uniformly which is unlikely to be the case. Under the direction of Dr. Walsh-Sukys, we have developed a protocol to define BPD by monitoring oxygen saturation that may be used to easily and safely standardize the definition of BPD across institutions (Appendix XI).

Secondary Outcomes:
1. Use of mechanical ventilation during the first 7, 14 and 28 days of life.
2. Frequency of apnea (cessation of breathing for >20 seconds).
3. Administration of oxygen and/or mechanical ventilation among survivors at 28 days of life.
4. Incidence of air leaks in the first 14 days of life (defined as pneumothorax, pneumopericardium, or pulmonary interstitial emphysema).

Incidence of intraventricular hemorrhage (Grade III or IV), periventricular leukomalacia, patent ductus arteriosus, sepsis, and retinopathy of prematurity.

Median lengths of hospital stay in survivors.

8d. Sample Size.

Based on the trials of Verder et al (133,134), we assume that treatment with CPAP will reduce the baseline incidence of BPD at 36 weeks by an absolute reduction of 5-10%. Using the CWRU database, we have approximately 200 neonates per year born weighing <1500 gm and a baseline incidence of BPD at 36 weeks of 26%. The table below indicates the numbers needed to detect a 5-15% absolute reduction at various initial incidence rates assuming a two-sided type I error rate of 0.05 and a power of 80%.

SAMPLE SIZE REQUIRED PER GROUP TO DETECT ABSOLUTE REDUCTIONS OF 5,10 AND 15%

	Initial BPD Incidence of 20%	Initial BPD Incidence of 25%	Initial BPD Incidence of 30%	Initial BPD Incidence of 35%
Reduction of 5%	904	1093	1249	1375
Reduction of 10%	199	250	293	328
Reduction of 15%	75	99	120	138

Thus, assuming all participating centers were equivalent in size to CWRU, a randomized trial performed at 16 centers would yield an available population of 3200 inborn VLBW infants per year. Since this trial focuses on those 601-1250 gm who are most at risk for BPD, the available population would be approximately 65% of that of all VLBW or 2080. If one assumes a 65% rate of consent for participation (the rate seen in the NICHD Neonatal Network Vitamin A Prevention Trial), then 1352 neonates could be recruited annually. Thus, the population of neonates available at 16 centers of a size comparable to that at CWRU would allow completion within 12-18 months of a study designed to detect a 5% absolute reduction in BPD.

8e. Data Analysis.

All data will be collected at the individual centers using standardized forms and electronic data entry. All analyses will be performed at the Central Data Center using the Intent to Treat method. Baseline population characteristics and

primary and secondary outcomes of the two randomized groups will be compared using Student's t-tests for continuous variables, and Chi-square tests for discrete variables. A type I error rate of 0.05 will be used in all tests of significance. All tests of significance will be two-sided. Multivariate analyses will be used to investigate possible associations between the primary and secondary outcome variables and the following: gestational age, birthweight, age at randomization, sex, antenatal steroid treatment, time of surfactant treatment, and treatment with caffeine.

Two interim analyses will be performed and reported to the Data Safety and Monitoring Committee with treatment groups masked (e.g., labeled only as Treatment A and Treatment B). Criteria for early discontinuation of the trial will be based on the method of Lans and De Mets with the use of the O'Brien-Fleming spending function.

8f. Ethical Considerations.

The protocol will be reviewed and approved by the Institutional Review Board at all participating institutions in accordance with the requirements of 45 CFR 46 (Protection of Human Subjects). Patients will be enrolled and randomized in the study only after informed permission is obtained from the neonate's parent or legal guardian. The patient's own physician will continue to function as the managing physician at all times, and may decline study participation or withdraw the patient from study participation at any time. Both nCPAP and mechanical ventilation are widely accepted treatments in routine use in neonatal intensive care. The primary risk to study patients is from apnea or air leaks. These risks will be minimized by careful monitoring with prompt interventions instituted, including the early use of caffeine that will be specified in a standardized management protocol.

Further protection of the research subjects from risk will be assured by the formation of an independent Data Safety and Monitoring Committee who will review the data at two planned interim analyses which will ensure that both anticipated and unanticipated adverse events are monitored and detected in a timely fashion. Procedures that maintain the confidentiality of the neonate and his/her family will be assured. All data will be collected under a coded system in which individual identifiers are maintained only at the individual center, and reported in coded fashion to the Central Data Registry.

8g. Participation of Minority Subjects.

Eligible subjects of all genders and races will be approached for participation. At CWRU, the racial composition of our VLBW population includes 50% Caucasian, 48% African-American and 2% Hispanic. As expected 52% of the population is male and 48% is female.

9. INTENT TO PARTICIPATE

The Case Western Reserve University-University Hospitals of Cleveland Center, categorically and without reservation enthusiastically expresses its intent to continue to participate in a cooperative manner with other Neonatal Research Network Clinical Centers, the NICHD, and the Data Center in all aspects of Network research.

The Center at Case Western Reserve University is extremely supportive of the Network. We have a highly qualified and enthusiastic Neonatal and Obstetric staff, including physicians, staff nurses, neonatal nurse practitioners, research nurses, pharmacists, social works, respiratory therapists together with the necessary support personnel, subspecialists and equipment committed and dedicated to continued participation in the Network. It has become standard practice for Network trials to be given the highest priority. We are resolute to continue this practice and are extremely proud of our past performance within the Network.

There is also unmistakable evidence of our ability to effectively accomplish all the goals of the Network and to collaborate with our Network colleagues. For almost 15 years we have demonstrated an ability to facilitate clinical trials, enroll patients, follow protocols, collect and transmit data, interpret the data, and prepare the data for publication. We have played a vital role in the administrative aspect of the Network through the Steering Committee, chairing the Generic Data Base, Publications, Intravenous Immune Globulin and Pulmonary Hypertension Committees, and serving on the Protocol Development, Ballard, Bilirubin, Follow-up, Growth, Necrotizing Enterocolitis, Nitric Oxide, and Surfactant Study Committees in addition to the Maternal-Fetal Network liaison and the Data Access

Committees. We have worked closely with the Data Center and transmitted data on thousands of patients since the inception of the Network. We are fully prepared to continue to do so.

10. DEPARTMENT AND INSTITUTIONAL COMMITMENTS

There is an unambiguous commitment to the Network from the Medical School, hospital administration, Departments of Pediatrics and Obstetrics as well as all the members of the Neonatal Division. There has been a commitment of space, resources, equipment and personnel to facilitate the research and fiscal administration of the grant. These are spelled out in the supporting letters.

Over the lifespan of the Network, the Department of Pediatrics and the School of Medicine have always been supportive in terms of space, facilities, and personnel. The Department of Pediatrics has been supportive of the Neonatal Follow-up Program, the various research endeavors in the Division that required supplemental support, and the Neonatal Fellowship Program. Indeed, the Department has been very supportive of clinical research with funds available for new investigators or established investigators who require additional support.

Within the Division of Neonatology the Principal Investigator is assisted by a Division Manager, who has responsibility for personnel, procurement, and budgetary matters. The Division Manager receives support from the Department of Pediatrics Administration, consisting of the Director of Finances, the Grants Manager, and the Administrator. These individuals report directly to the Chairman of the Department of Pediatrics. The Director of Finances is responsible for department-wide fiscal matters, the Grants Manager acts as liaison between the divisions and the Business Office of Case Western Reserve University School of Medicine, and assists investigators in adhering to NIH and other grant agencies' requirements, and the administrator provides support in personnel and logistical matters.

Perinatal Medicine remains one of the top priorities and an integral part of the long range plan for University Hospitals of Cleveland. The facilities and equipment have been recently upgraded for both Obstetrics and Neonatology. New labor, delivery and recovery rooms have been constructed; central fetal monitoring has been installed and, through insurance and managed care contracts, the hospital has ensured the vitality of the Obstetric service. The neonatal monitors have all been replaced in the neonatal intensive care unit within the past year and a new step down unit with sleep facilities for babies and their parents has been open for the past three years. Our administration has willingly, at all times, provided the resources to render superb care to all patients, irrespective of payor class. They also understand the importance of, and are committed to, clinical research.

We, therefore, have the moral, physical, and financial backing from the Department of Pediatrics, University Hospitals of Cleveland, and Case Western Reserve University School of Medicine.

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by: FANAROFF, Dr. A.A. et al.

Entitled: Randomized Controlled Trial of Induced Hypothermia for Hypoxic-Ischemic Encephalopaty in Term Newborns (06-99-29)

Please be advised that with respect to : (1) The rights and welfare of individuals
(2) The appropriateness of the methods used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

_XXX FULLY ACCEPTABLE, without reservation; approved through _5/2001__

_____NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence
Approved Under 45CFR46.405
DELETION: S. Bergant

May 16, 2000
Date(s) of Committee Review

May 16, 2000
Date of Approval

Signature IRB Chairman

TYPE PROJECT ( ) New (X) Renewal ( ) Addendum

HUMAN RISK (X) Yes ( ) No

SOURCE OF SUPPORT ( ) None ( ) Departmental (X) Outside Funding

Agency (Potential) NIH-NICHD Agency Number 642-5182

ARE ANY OF THE FOLLOWING INVOLVED? ( ) No (X) Yes, those checked

X Minors __Fetuses __Abortuses __Prisoners __Pregnant Women __Mentally Retarded __Mentally Disabled

CC: Investigator, ORA, General Clinical Research Center

The UHC IRB operates under the HHS Multiple Project Assurance of Compliance Number M1521 02

Rev. 01/97

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by: FANAROFF, Dr. A.A. et al.

Entitled: Randomized Controlled Trial of Induced Hypothermia for Hypoxic-Ischemic Encephalopaty in Term Newborns (06-99-29)

Please be advised that with respect to : (1) The rights and welfare of individuals
(2) The appropriateness of the methods used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

XXX FULLY ACCEPTABLE, without reservation; approved through _5/2001_

_____NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence
Approved Under 45CFR46.405
DELETION: S. Bergant

May 16, 2000
Date(s) of Committee Review

May 16, 2000
Date of Approval

Signature IRB Chairman

TYPE PROJECT ( ) New (X) Renewal ( ) Addendum

HUMAN RISK (X) Yes ( ) No

SOURCE OF SUPPORT ( ) None ( ) Departmental (X) Outside Funding

Agency (Potential) NIH-NICHD Agency Number 642-5182

ARE ANY OF THE FOLLOWING INVOLVED? ( ) No (X) Yes, those checked

X Minors __Fetuses __Abortuses __Prisoners __Pregnant Women __Mentally Retarded __Mentally Disabled

CC:Investigator, ORA, General Clinical Research Center

The UHC IRB operates under the HHS Multiple Project Assurance of Compliance Number M1521 02

Rev. 01/97

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by: FANAROFF, Dr. A.A. et al.

Entitled: Immediate Extubation After the First Dose of Surfactant to Reduce the Use of Mechanical Ventilation (03-00-36)

Please be advised that with respect to : (1) The rights and welfare of individuals
(2) The appropriateness of the methods used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

XXX FULLY ACCEPTABLE, without reservation; approved through _4/2001_

_____NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence
Approved Under 45 CFR 46.405

March 21, 2000
Date(s) of Committee Review

April 24, 2000
Date of Approval

John R Dunphy MD
Signature IRB Chairman

TYPE PROJECT (X) New ( ) Renewal ( ) Addendum

HUMAN RISK (X) Yes ( ) No

SOURCE OF SUPPORT ( ) None ( ) Departmental (X) Outside Funding

Agency (Potential) NIH-NICHD Agency Number 642-5182

ARE ANY OF THE FOLLOWING INVOLVED? ( ) No (X) Yes, those checked

X Minors __Fetuses __Abortuses __Prisoners __Pregnant Women __Mentally Retarded __Mentally Disabled

CC: Investigator, ORA, General Clinical Research Center

The UHC IRB operates under the HHS Multiple Project Assurance of Compliance Number M1521 02

Rev. 01/97

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND

INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by FANAROFF, Dr. A. A.

Entitled: Are Inflammatory Cytokines Associated with Perinatal Brain Injury and Long Term Neurodevelopmental Handicap? (04-00-26)

Please be advised that with respect to : (1) The rights and welfare of individuals
(2) The appropriateness of the methods used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

XXX FULLY ACCEPTABLE, without reservation; approved through _5/2001_

_____NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence
Expedited Approval
Modification to Checklist
Modification to Consent Form
Approved Under 45CFR 46.404

Date(s) of Committee Review

May 22, 2000
Date of Approval

John R. Murphy MD
Signature IRB Chairman

TYPE PROJECT (X) New ( ) Renewal ( ) Addendum

HUMAN RISK (X) Yes ( ) No

SOURCE OF SUPPORT ( ) None ( ) Departmental (X) Outside Funding

Agency (Potential) NIH- NCHD Agency Number 642-5182

ARE ANY OF THE FOLLOWING INVOLVED? ( ) No (X) Yes, those checked

_X_Minors __Fetuses __Abortuses __Prisoners __Pregnant Women __Mentally Retarded __Mentally Disabled

CC: Investigator, ORA, General Clinical Research Center

The UHC IRB operates under the HHS Multiple Project Assurance of Compliance Number M1521 02

Rev. 01/97

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by FANAROFF, Dr. A. A.

Entitled: Randomized Trial of Parental Glutamine Supplementation for Extremely Low Birth-weight Infants (05-99-03)

Please be advised that with respect to : (1) The rights and welfare of individuals
(2) The appropriateness of the methods used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

XXX FULLY ACCEPTABLE, without reservation; approved through _6/2001_

_____NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence
Approved Under 45 CFR 46.405

May 16, 2000
Date(s) of Committee Review

June 16, 2000
Date of Approval

Signature IRB Chairman

TYPE PROJECT ( ) New (X) Renewal ( ) Addendum

HUMAN RISK (X) Yes ( ) No

SOURCE OF SUPPORT ( ) None ( ) Departmental (X) Outside Funding

Agency (Potential) NIH- NCHD Agency Number 642-5182

ARE ANY OF THE FOLLOWING INVOLVED? ( ) No (X) Yes, those checked

_X_Minors __Fetuses __Abortuses __Prisoners __Pregnant Women __Mentally Retarded __Mentally Disabled

CC: Investigator, ORA, General Clinical Research Center

The UHC IRB operates under the HHS Multiple Project Assurance of Compliance Number M1521 02

Rev. 01/97

EXAMPLE

UNIVERSITY HOSPITALS OF CLEVELAND
INSTITUTIONAL REVIEW BOARD FOR HUMAN INVESTIGATION

TO: Dr. E. Avner
Department Chairman

The University Hospitals Institutional Review Board has reviewed the proposal

Submitted by: FANAROFF, Dr. A.A. et al.

Entitled: Is delayed clamping of the umbilical cord at the time of delivery beneficial for extremely low birthweight (ELB) infants?(05-99-02)

Please be advised that with respect to:
(1) The rights and welfare of the individuals
(2) The appropriateness of the methods to be used to secure informed consent
(3) The risks and potential medical benefits of the investigation the Board considers this project

☒ FULLY ACCEPTABLE, without reservation; approved through 08/2000

☐ NOT ACCEPTABLE for reasons noted

REMARKS:

The annual review is due by the date noted above.
Please reference the IRB number on future reviews and correspondence

May 4, 1999
Date(s) of Committee Review

August 18, 1999
Date of Approval

Signature IRB Chairman

TYPE PROJECT ☒ New ☐ Renewal ☐ Addendum

HUMAN RISK ☒ Yes ☐ No

SOURCE OF SUPPORT: ☐ None ☐ Departmental ☐ Outside Funding

Agency (Potential) _____ Agency Number _____

ARE ANY OF THE FOLLOWING INVOLVED? ☐ No ☒ Yes, those checked

☒ Minors ☐ Fetuses ☐ Abortuses ☐ Prisoners ☐ Pregnant Women ☐ Mentally Retarded ☐ Mentally Disabled

C: Investigator, ORA, General Clinical Research Center

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134. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, Agertoft L, Djernes B, Nathan E, Reinholdt J: Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 103:e24, 1999.

CASE WESTERN RESERVE UNIVERSITY

July 3, 2000

Dr. Avroy Fanaroff
Div. of Neonatology
Rainbow Babies & Children's Hospital
11100 Euclid Avenue
Cleveland, OH 44106

Dear Dr. Fanaroff,

It will be a pleasure to continue to participate in the Follow-up component of the NICHD Neonatal Research Network, including both the generic follow-up of all surviving < 1000 gm birth weight infants and in the follow up of infants who participate in specific studies and randomized controlled trials.

As you know, our program has, to date, had the best follow up rate of the participating Network Centers with a return rate of over 90%. Furthermore, Dr. Wilson-Costello serves on the Follow Up Committee and Mrs. Harriet Friedman, Developmental Specialist serves as a "Gold Standard" tester for the Bayley Scales of Infant Development.

We look forward to a continued active participation in the follow up studies of the Neonatal Network.

Sincerely,

Maureen Hack

Maureen Hack, M.D.
Professor of Pediatrics
Director of High Risk Follow-up

/cal

A:\Hack\Disk 5 \Fanaroffletter\7/3/00:cal

Maureen Hack, M.D.
Department of Pediatrics
School of Medicine
Case Western Reserve University

MAILING ADDRESS
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland, Ohio 44106

Phone 216-844-3387
Fax 216-844-3380
Email mxh7@po.cwru.edu

UniversityHospitals
HealthSystem

CASE WESTERN RESERVE UNIVERSITY

Rainbow Babies
& Children's Hospital

Claire M. Doerschuk, MD
Professor of Pediatrics
Vice-Chair for Research
Chief, Division of Integrative Biology

July 3, 2000

Charlotte S. Catz, M.D.
NICHD
Landow Building, Room 7009
Bethesda, MD 20205

Dear Dr. Catz:

As the Vice-Chair of Research for the Department of Pediatrics, I am delighted to support Dr. Fanaroff's application for the Cooperative Multicenter Neonatal Research Network. This Network has already proven invaluable and critical in identifying and investigating many critical issues in neonatal medicine, most of which could not be addressed except in the context of a multicenter, multidisciplinary team. Our Department has a long-term commitment to translate basic research into clinical benefits, and the Network is an outstanding opportunity to identify clinical issues for research at the bench and for testing basic research concepts at the bedside.

Our Division of Neonatology has always been strongly committed to the cutting-edge application of new discoveries to benefit patients, as well as to define the research questions that are of interest for pursuit in the research laboratories. They have an outstanding track record in clinical research, basic science research and translational studies. We are delighted to have the opportunity to participate in the neonatal research network.

The Research Office of our Department is fully supportive and will provide the infrastructure necessary for efficient operation of this grant.

Please let me know if I can provide any other information in support of this application. Thank you very much. With very best wishes, I remain,

Yours sincerely,

Claire M. Doerschuk, M.D.
Professor of Pediatrics
CMD:ve
c:\wp\reconm-ltrs\catz.j03

Rainbow Babies and Children's Hospital, Room 8321 11100 Euclid Avenue Cleveland, Ohio 44106-6003
Phone 216-844-3669 FAX 216-368-5570 e-mail: cmd22@po.cwru.edu

University Hospitals Health System

MacDonald
Women's Hospital

Gail C. Larson
Senior Vice President
General Manager

June 30, 2000

Charlotte S. Catz, M.D.
National Institute of Child Health and Human Development
Landow Building, Room 7009
Bethesda, MD 20205

Dear Dr. Catz:

As Senior Vice President and General Manager for Women's and Children's Services at University Hospitals of Cleveland, I am pleased to endorse, without reservation, this grant application submitted in response to the National Institute of Child Health and Human Development announcement.

The Principal Investigator, Dr. Avroy A. Fanaroff, has a long and distinguished record and is eminently qualified to carry out the proposal. The research proposal has the full support of MacDonald Women's Hospital and Rainbow Babies and Children's Hospital. Our institution would be proud to be a participant in this most worthwhile cooperative effort.

Sincerely,

Gail C. Larson

11100 Euclid Avenue Cleveland, Ohio 44106-6003 Phone 216-844-3762 FAX 216-844-5179

Laszlo Sogor, MD, PhD
Chief of Gynecology
Department of Ob-Gyn
Associate Professor, Reproductive Biology
CWRU School of Medicine

UniversityHospitals HealthSystem

MacDonald Women's Hospital

CASE WESTERN RESERVE UNIVERSITY

June 23, 2000

Avroy Fanaroff, MD
Department of Pediatrics
Division of Neonatology
Rainbow Babies & Childrens Hospital
RBC 6010

Dear Dr. Fanaroff:

I fully support and endorse the enclosed application for the Cooperative Multicenter Neonatal Research Network. As Acting Chairman of Reproductive Biology at Case Western Reserve University, and Director of the Department of Obstetrics and Gynecology at University Hospitals, I am fully committed to the ongoing development of a very strong maternal-fetal section to be in a position to perform independent and collaborative research projects. We strongly believe in the concept of multicenter trials and are committed to the success of this project.

Sincerely,

Laszlo Sogor, M.D., Ph.D

LS:mr

Department of Obstetrics and Gynecology / Department of Reproductive Biology, CWRU
11100 Euclid Avenue Cleveland, Ohio 44106 216-844-1692 FAX 216-844-7590
MacDonald Women's Hospital is part of University Hospitals of Cleveland, the Primary Affiliate of Case Western Reserve University

University Hospitals
Health System

Rainbow Babies
& Children's Hospital

June 27, 2000

Avroy A. Fanaroff, M.D.
Professor
Department of Pediatrics
Case Western Reserve University

RE: Cooperative Multicenter Neonatal Research Network

Dear Doctor Fanaroff:

I am writing to express my full support and endorsement for your application for renewal of your participation in the Cooperative Multicenter Neonatal Research Network. As Chief of the Division of Pediatric Pharmacology and Critical Care at Rainbow Babies and Childrens Hospital, I am committed to the ongoing cooperation between the cooperative neonatal research program and our programs in critical care and pediatric pharmacology. Over the years a true synergy has developed among these activities, which has broadened our collective research capabilities and enhanced patient care.

Our relationship has been augmented by the awarding of one of the NIH-funded Pediatric Pharmacology Research Units (PPRU) to us in the Division of Pediatric Pharmacology and Critical Care. Whereas in the past we have pledged our support for all of those research activities sponsored by the Neonatal Network that involve drugs, under the auspices of the PPRU we are now able to commit more extensive resources in support of these activities.

Overall our group compliments the research strength and experience already present in your Neonatal Research Unit and we are excited by the prospects to continuing collaboration.

Sincerely,

Jeffrey L. Blumer, Ph.D., M.D.
Professor of Pediatrics and Pharmacology
Case Western Reserve University
Chief, Division of Pediatric Pharmacology
And Critical Care
Rainbow Babies and Childrens Hospital

11100 Euclid Avenue Cleveland, Ohio 44106

Division of Maternal-Fetal Medicine
Phone: 216-844-8267
Fax: 216-844-7590
Mail Stop 5034

University Hospitals Health System

MacDonald Women's Hospital

CASE WESTERN RESERVE UNIVERSITY

June 23, 2000

Charlotte S, Catz, M.D.
National Institute of Child Health and Human Development
Landow Building, room 7009
Bethesda, MD 20205

RE: Cooperative Multicenter Neonatal Research Network

Dear Dr. Catz:

We fully support and endorse the enclosed application for the Cooperative Multicenter Neonatal Research Network. As members of the Department of Reproductive Biology at Case Western Reserve University, and the Department of Obstetrics and Gynecology at University Hospitals, We are fully committed to the ongoing development of a very strong maternal-fetal section to be in a position to perform independent and collaborative research projects. We strongly believe in the concept of multicenter trials and are committed to the success of this project.

Yours Sincerely,

Robert Kiwi, M.D.

Dinesh M. Shah, M.D.

Nancy E. Judge, M.D.

Kevin Muise, M.D.

:jly

Department of Obstetrics and Gynecology / Department of Reproductive Biology, CWRU
11100 Euclid Avenue Cleveland, Ohio 44106 216-844-3334 FAX 216-844-7590
MacDonald Women's Hospital is part of University Hospitals of Cleveland, the Primary Affiliate of Case Western Reserve University

UniversityHospitals HealthSystem

Rainbow Babies & Children's Hospital

CASE WESTERN RESERVE UNIVERSITY
School of Medicine

Ellis D. Avner, MD
The Gertrude Lee Chandler Tucker
Professor and Chairman
Pediatrician-in-Chief

July 3, 2000

Charlotte S. Catz, M.D.
National Institutes of Child Health and
Human Development
Landow Building, Room 7009
Bethesda, MD 20205

Dear Dr. Catz:

As Chairman of the Department of Pediatrics at Case Western Reserve University School of Medicine, it is with great enthusiasm that I endorse the grant application being submitted by Avroy A. Fanaroff, M.D.

The contributions made by the Cooperative Multicenter Network have helped to resolve medical problems of the critically ill neonates in the Neonatal Intensive Care Unit. We at Rainbow Babies & Children's Hospital are deeply committed to excellence of patient care, and support our faculty in their teaching and research endeavors. The members of the Division of Neonatology, in this project, will expand their research productivity as well as improve patient care.

The resources and support of the Department of Pediatrics at Rainbow Babies & Children's Hospital are at the disposal of Dr. Fanaroff and the Division of Neonatology.

Sincerely,

Ellis D. Avner, M.D.
Professor and Chairman
Department of Pediatrics

EDA/mlg

Department of Pediatrics 11100 Euclid Avenue Cleveland, Ohio 44106 Phone 216-844-3884 FAX 216-844-1479 e-mail: eda@po.cwru.edu

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

[x] NEW application. *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

[X] COMPETING CONTINUATION of grant number: HD21364
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl. only)*
[X] No [ ] Previously reported
[ ] Yes. If "Yes," [ ] Not previously reported

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

[ ] FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS
The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

-Human Subjects; -Vertebrate Animals; -Debarment and Suspension; -Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; - Lobbying; -Delinquent Federal Debt; -Research Misconduct; -Civil Rights (Form HHS441 or HHS 690); -Handicapped Individuals (Form HHS 641 or HHS 690); -Sex Discrimination (Form HHS 639-A or HHS 690); -Age Discrimination (Form HHS 680 or HHS 690); -Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 20.)*
All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
4/1/01 - 3/30/06	$644,621	NIH

3. INDIRECT COSTS
Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal Agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates*, and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. F & A costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Awards, and specialized grant applications.

[x] DHHS Agreement dated: 05/03/99 [ ] No F&A Costs Requested.

[ ] DHHS Agreement being negotiated with _____ Regional Office

[ ] No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on F & A costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base: $ 122,276 x Rate applied 53% % = F&A costs (1) $ 64,806

b. Entire proposed project period: Amount of base: $ 644,621 x Rate applied 53% % = F&A costs (2) $ 341,649

(1) Add to total direct costs from form page 4 and enter new total on FACE PAGE, item 7b.
(2) Add to total direct costs from form page 5 and enter new total on FACE PAGE, item 8b.

*Check appropriate box(es):

[ ] Salary and wages base [X] Modified total direct cost base [ ] Other base *(Explain)*
[ ] Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.)*:

4. SMOKE-FREE WORKPLACE
Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?

[X] Yes [ ] No *(The response to this question has no impact on the review or funding of this application.)*

AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services

6 9 1 8 2 2

JUL 11 2

* PI: DONOVAN, EDWARD
Grant #: 1 U10 HD027853-11
Dual:
IRG: ZHD1 SRC(99)

Council: 01/2001

PP

Received: 07/11/2000

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

1. TITLE OF PROJECT

Cooperative Multicenter Neonatal Research Network

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*

Numbe **HD-00-010** Title: **Cooperative Multicenter Neonatal Research Network**

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR New Investigator ☐ Yes

3a. NAME *(Last, first, middle)*	3b. DEGREE(S)	3c. SOCIAL SECURITY NO.
Donovan Edward F.	**M.D.**	**Provide on Form Page KK**

3d. POSITION TITLE
Professor

3e. MAILING ADDRESS *(Street, city, state, zip code)*
Department of Pediatrics
University of Cincinnati
PO Box 670541
Cincinnati, Ohio 45267-0541

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Pediatrics

3g. MAJOR SUBDIVISION
College of Medicine

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: **(513) 558-0381**
FAX: **(513) 558-7770**

E-MAIL ADDRESS:
donovaef@email.uc.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date	Full IRB or Expedited Review	4b. Assurance of compliance No.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval	5b. Animal welfare assurance no.
☐ No ☒ Yes	attached	☐	M-1138	☒ No ☐ Yes		A3295-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year-MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
04/01/01	03/31/06	126,100	192,933	667,318	1,020,996

9. APPLICANT ORGANIZATION
Name **University of Cincinnati**
Address **PO Box 670553**
Cincinnati, Ohio 45267-0553

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE **01**

12. ENTITY IDENTIFICATION NUMBER **1316000989A1**
DUNS NO. (if available) **041064767**
Congressional District **1 & 2**

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name **John Michnowicz**
Title **Director, Office of Sponsored Programs**
Address **University of Cincinnati**
Cincinnati, Ohio 45267-0553
Telephone **(513) 558-3683**
FAX **(513) 558-3954**
E-Mail **ospaward@uc.edu**

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name **John Michnowicz**
Title **Director, Office of Sponsored Programs**
Address **University of Cincinnati**
Cincinnati, Ohio 45267-0553
Phone **(513) 558-3683**
FAX **(513) 558-3954**
E-Mail **john.michnowicz@uc.edu**

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
Edward F. Donovan M.D.

DATE
6/28/00

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)*

DATE
6/29/00

University of Cincinnati
Medical Center

College of Medicine
Department of Pediatrics

Division of Neonatology
University of Cincinnati
PO Box 670541
Cincinnati OH 45267-0541

231 Bethesda Avenue
Phone (513) 558-5341
Fax (513) 558-7770

STATEMENT FOR THE ACCEPTANCE OF BUDGETARY MECHANISMS

The Department of Pediatrics and the University of Cincinnati understand that reimbursement of protocol budgets will be computed on the actual versus the anticipated number of enrolled patients, which were used to develop these budgets. It is further understood that reimbursement will not exceed the awarded amount based on the anticipated enrollment without prior negotiation with the NICHHD staff.

Jeffrey A. Whitsett, M.D., Director
Division of Neonatology

6/25/00
John Michnowicz, Director
Office of Sponsored Programs

HUMAN SUBJECTS:

Neonatal Research Network

Early Inhaled Nitric Oxide Study	IRB #	Last approval date
University Hospital	98-9-6-C	02/09/00
Children's Hospital	98-9-6	10/28/99
Good Samaritan Hospital	307	03/31/00
Glutamine Study		
University Hospital	99-7-2-1	09/15/99
Children's Hospital	99-7-3	07/19/99
Good Samaritan	320	09/23/99
Hypothermia		
University Hospital	99-09-01-02	05/10/00
Children's Hospital	99-9-1	03/31/00
Good Samaritan	175GS	09/24/99*
		*6 month approval
Early vs. Late Cord Clamping		
University Hospital	00-3-28-2	approval pending
Surfactant/CPAP		
University Hospital	00-4-24-2	approval pending
Children's Hospital	00-4-6	06/06/00
Good Samaritan	2000.04015GS	03/31/00
Follow up Protocol		
University Hospital	96-7-9-02	08/26/99
Children's Hospital	95-1-8X	04/11/00
Good Samaritan Hospital	140	09/24/99

DESCRIPTION: State the applicant's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplsihments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the applicantion is funded, this description, as is, will become public information. **DO NOT EXCEED THE SPACE PROVIDED.**

The Division of Neonatology of the Department of Pediatrics at the University of Cincinnati and the Children's Hospital Medical Centers is applying to continue to be a part of the NICHD Neonatal Research Network. Our major strengths are the following: 1) a large NICU population that includes all NICU admissions in a 9,544 square mile region with 30,000 annual births; 2) a philosophically and academically integrated group of neonatologists providing care throughout the region; 3) a unique, community-wide, integrated, and fully operational Neonatal/Perinatal Outreach Network; 4) a strong commitment and track record of excellence in federally funded, investigator-initiated and center-grant-related research, both basic and clinical; 5) unique, ultramodern NICU facilities; 6) a longstanding, documented collaboration with our Maternal-Fetal Medicine Division in clinical care, research and training including a Cincinnati NIH MFMU Network; 7) a large and reputable Neonatology research fellowship with NIH funding; 8) a large group of exceptionally talented neonatologists, all committed to our contribution to the NICHD Neonatal Research Network; and 10) a documented track record of collaborative research with other centers. We believe that the above mentioned strengths make us an excellent candidate for continuation in the NICHD Neonatal Research Network.

PERFORMANCE SITE(S) (organization, city, state)

University of Cincinnati Medical Center, Cincinnati, Ohio
University Hospital NICU, Cincinnati, Ohio
Children's Hospital RCNIC, Cincinnati, Ohio
Good Samaritan Hospital NICU, Cincinnati, Ohio

KEY PERSONNEL.

Name	Organization	Role on Project
Edward F. Donovan, M.D.	University of Cincinnati	Principal Investigator
Barbara Warner, M.D.	Children's Hospital	Co-Principal Investigator
Jean J. Steichen, M.D.	University of Cincinnati	Collaborator
Beth Haberman, M.D.	Children's Hospital	Collaborator
Baha Sibai, M.D.	University of Cincinnati	Collaborator
Jon Fridriksson, M.D.	Children's Hospital	Collaborator
Alan Jobe, M.D.	Children's Hospital	Consultant
James Heubi, M.D.	Children's Hospital	Consultant
Tariq Siddiqi, M.D.	University of Cincinnati	Collaborator

MULTICENTER NETWORK OF NEONATAL INTENSIVE CARE UNITS
5 U10 HD27853

TABLE OF CONTENTS

DD | Principal [redacted]gator/Program Director(Last, first, middle): [redacted] **Donovan, Edward**

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM **4/1/2001** THROUGH **3/31/2002**

PERSONNEL (Applicant organization only) NAME	ROLE ON PROJECT	TYPE APPT. (MONTHS)	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED (omit cents) SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Edward Donovan, M.D.	Principal Investigator	#	%	$	**$11,520**	**$3,410**	**$14,930**
Marcia Mersmann	**Res. Nurse Coord.**				**$53,735**	**$14,562**	**$68,297**
Michele Boshko	**Data entry Clerk**				**$13,571**	**$4,302**	**$17,873**
	SUBTOTALS				**$78,826**	**$22,274**	**$101,100**

CONSULTANTS COSTS		**$0**
EQUIPMENT (Itemize)		**$0**
Supplies (Itemize by category)		
File cabinet (locking)	**500**	
Computer system	**3,100**	
Specialized paper	**400**	
Printing/artwork	**500**	
		$4,500
TRAVEL		
Ten trips to Bethesda, Maryland for Network Team Meetings - $1,800 per trip		**$18,000**
PATIENT CARE COSTS — INPATIENT		**$0**
PATIENT CARE COSTS — OUTPATIENT		**$0**
ALTERATIONS AND RENOVATIONS (Itemize by category)		**$0**
OTHER EXPENSES (Itemize by category)		
Patient recruitment/tracking and incentives	**2,500**	
		$2,500
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD		**$126,100**
CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS		
CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATION COSTS		
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(ITEM 7A, FACE PAGE)*		**$126,100**

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 3a., 3b.

= Months Dedicated to Project

$ = Institutional Based Salary

% = Percentage of Effort

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD

DIRECT COSTS ONLY

JDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD (from page 4)	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL: Salary and fringe benefits Applicant organization only		**$101,100**	**$104,133**	**$107,257**	**$110,475**	**$113,789**
CONSULTANT COSTS						
EQUIPMENT						
SUPPLIES		**$4,500**	**$4,500**	**$4,500**	**$4,500**	**$4,500**
TRAVEL		**$18,000**	**$18,540**	**$19,096**	**$19,669**	**$20,259**
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
OTHER COSTS		**$2,500**	**$2,500**	**$2,500**	**$2,500**	**$2,500**
SUBTOTAL DIRECT COSTS		**$126,100**	**$129,673**	**$133,353**	**$137,144**	**$141,048**
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
	F& A					
TOTAL DIRECT COSTS		**$126,100**	**$129,673**	**$133,353**	**$137,144**	**$141,048**
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD (Item 8a)						**$667,318**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

*** Ms. Boschko's current official appointment is 80% FTE. Therefore, she will devote 62.5% of her time working on this grant.**

Salaries and travel budgets will increase by 3% each year.
Supplies and other expenses will remain the same for the entire project period per RFA.

Fringe Benefit rates for year 1:

Dr. Donovan	**30%**
Ms. Mersmann	**27%**
Ms. Boshko	**32%**

BUDGET JUSTIFICATION

Supplies:

File cabinet (locking): Storage of confidential research related patient records as required by NICHD	$500
Computer system – including software, monitor and printer for development and storage of Network research materials	$3100
Specialized papers to be utilized in creation of study brochures and related materials necessary for optimal patient recruitment and enrollment	$400
Printing/artwork: of study related materials for education of staff and parents	$500
TOTAL	$4,500

Other expenses:

Patient recruitment/tracking: Mailings, etc. for continuing parent contact and explanation of studies; incentives for compliance with follow-up requirements, etc.	$2500

The University of Cincinnati GCRC provided more than $35,000 in support of 5 different Neonatal Research Network studies over the last five years.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
EDWARD F. DONOVAN	PROFESSOR OF PEDIATRICS & OBSTETRICS & GYNECOLOGY

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Stanford University, Palo Alto, California	B.A.	1967	Psychology
U.C.L.A. Medical School, California	M.D.	1971	Medicine
Children's Hospital Medical Center, Cincinnati		1973	Pediatric Residency
University of Cincinnati College of Medicine	Fellow	1977	Newborn Physiology
McGill University, Montreal, Canada		1978	Respiratory Physiology
University of Michigan, SPH, Ann Arbor, Michigan		1994-present	Doctoral student in Health Policy & Health Serv Res

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

RESEARCH AND PROFESSIONAL EXPERIENCE

Assistant Professor of Pediatrics & Obstetrics & Gynecology, 1977-1984
Medical Director of Respiratory Therapy, Children's Hospital Medical Center, 1978-1987
Director, Regional Center for Newborn Intensive Care, Children's Hospital Medical Center, 1983-1990
Director, Neonatal Transport Service, Children's Hospital Medical Center, 1980-1995
Director, Regional Neonatology Consultation Services, Children's Hospital Medical Center, 1990-1995
Assoc Professor of Clinical Pediatrics and Obstetrics and Gynecology, University of Cincinnati College of Medicine, 1984-1996
Professor of Pediatrics, Obstetrics & Gynecology, University of Cincinnati College of Medicine, 1996-present
Principle Investigator, Neonatal Research Network, National Institute of Child Health Department
Program Director, Women's & Children's Health Outcomes Program, Child & Family Health Services, Ohio Department of Hlth
Director, Child Health Statistics Center, 1998-present

PUBLICATIONS (since 1998)

1. Papile, L.A., Tyson, J.E., Stoll, B.J., Wright, L.L., Donovan, E.F., et al: Multi-center trial of two Dexamethasone therapy regimens in ventilator-dependent premature infants. NEJM 338:1112-1118, 1998.
2. Donovan, E.F., Ehrenkranz, R.A., Shankaran, S., et al: Outcomes of very low birth weight twins cared for in the NICU. AJOG 179(3 Pt1):742-749, 1998.
3. Donovan, E.F. Practice variation: Implications for neonatal red blood cell transfusions. Editorial. J Pediatr 133(5):589-599, 1998.
4. Stevenson, D.K., Wright, L.L., Lemons, J.A., Oh, W., Korones, S.B., Papile, L.A., Bauer, C.R., Stoll, B.J., Tyson, J.E., Shankaran, S., Fanaroff, A.A., Donovan, E.F., et al: Very low birth weight outcomes of the NICHD Neonatal Research Network, January 1993 through December 1994. AJOG 179:1632-1639, 1998.
5. Donovan, E.F., Schwartz, J.E., Moles, L.M.: New technologies applied to the management of respiratory dysfunction. In: Comprehensive Neonatal Nursing Care: A Physiologic Perspective, Kenner, Gunderson and Brueggemeyr (eds), W.B. Saunders Co., Philadelphia, Chpt 19, 268-289, 1998.
6. How, H., Donovan, E., Khoury, J., et al. The effects of antenatal corticosteroid (CS) on the outcome of very low birth weight infants (VLBW). AJOG 178(1pt2):659. (presented)
7. Stoll, B.J., Temprosa, M.G., Tyson, J.E., Papile, L.A., Wright, L.L., Donovan, E.F., et al. Infections among very low birthweight infants enrolled in the NICHD Neonatal Research Network dexamethasone (Dex) trial. Pediatric Res 43:253A, 1998. (presented)
8. Khan, A.O., Mermann, M.A., Donovan, E.F., West, C.E. Clinical utility of a computer program in predicting threshold retinopathy of prematurity. JAAPOS 1998. (presented)

9. Musial, J., Warner, B., Donovan, E., Atherton,H. A regional perinatal database supports 'The guidelines for perinatal care' recommendations for maternal transport. Ped Res 1998.
10. Donovan, E., Zhou, J., Dooley, P. Return-on-investment of prenatal interventions designed to reduce low-birth-weight: An economic policy perspective. Ped Res 102:760, 1998. (presented)
11. Tyson, J.E., Wright, L.L., Oh, W., Kennedy, K.A., Mele, L., Ehrenkranz, R.A., Stoll, B.J., Lemons, J.A., Stevenson, D.K., Bauer, C.R., Korones, S.B., Fanaroff, A.A., Donovan, E.F., et al: A multi-center randomized trial of vitamin A supplementation for extremely low birth weight infants. New England Journal of Medicine 340:1962-1968, 1999.
12. Stoll, B.J., Temprosa, M., Tyson, J.E., Papile, L.A., Wright, L.L., Bauer, C.R., Donovan, E.F., et al. Dexamethasone therapy increases infection in very low birth weight infants. Pediatrics 104(5):e63(electronic), 1999.
13. Ehrenkranz, R.A., Younes, N., Lemons, J.A., Fanaroff, A.A., Donovan, E.F., et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 104(2):280-289, 1999.
14. Demarini, S., Dollberg, S., Hoath, S.B., Ho, M., Donovan, E.F. Effects of antenatal corticosteroids on blood pressure in very low birth weight infants during the first 24 hours of life. J Perinatology 19(6):419-425, 1999
15. Donovan, E.F., Tyson, J.E., Ehrenkranz, R.A., et al. Inaccuracy of the new Ballard score before 29 weeks gestation. J Pediatrics 135(2):147-152, 1999.
16. McCain, G.D., Donovan, E.F., Gartside, P. Preterm infant behavioral and heart rate responses to antenatal phenobarbital. Research in Nursing and Health 22(6):461-470, 1999.
17. Donovan, E.F., Schwartz, J.E., Moles, L.M. New technologies applied to the management of respiratory dysfunction. In: Comprehensive Neonatal Nursing Care: A Physiologic Perspective, Kenner, Gunderson and Brueggemeyr (eds), W.B. Saunders, Co., Philadelphia, Chpt 19, 268-289, 1998.
18. Carlo, W.A., Stark, A.R., Bauer, C., Donovan, E.F., et al. Effects of minimal ventilation in a multicenter randomized controlled trial of ventilator support and early corticosteroid therapy in extremely-low-birth-weight infants. Pediatr Res 104:739, 1999. (presented)
19. Stark, A.R., Carlo, W.A., Bauer, C., Donovan, E.F., et al. Complications of early steriod therapy in a randomized controlled trial. Pediatr Res 104:738, 1999. (presented)
20. Ohls, R.K., Ehrenkranz, R.A., Lemons, J.A, Korones, S.B., Stoll, B.J., Stark, A.R., Wright, L.L., Shankaran, S., Donovan, E.F., et al. A multicenter randomized double-masked placebo-controlled trial of erythropoietin and iron administration to preterm infants $\leq$ 1250 grams birthweight. Ped Res, 1999. (presented)
21. Ohls, R.K., Ehrenkranz, R.A., Lemons, J.A., Korones, S.B., Stoll, B.J., Stark, A.R., Wright, L.L., Shankaran, S., Donovan, E.F., et al. A multicenter randomized double-masked placebo-controlled trial of early erythropoietin and iron administration to preterm infants. Ped Res, 1999. (presented)
22. Walsh-Sukys, M.C., Fanaroff, A.A,. Bauer, C.R., Korones, S.B., Stevenson, D.K., Tyson, J.E., Verter, J., Wright, L.L., Stoll, B.J., Lemons, J.A., Papile, L.A., Donovan, E.F., et al. Persistent pulmonary hypertension of the newborn (PPHN) in the era before nitirc oxide: practice variation and outcomes. Pediatrics 105:14-20, 2000.
23. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes. Pediatrics 105(2):295-310, 2000.
24. Warner, B.B., Musial, J., Kiely, J., Chenier, T., Donovan, E. Delivery site and very low birth weight outcomes. Ped Res 47(4):328A, 2000. (poster presentation)
25. Haberman, B., Donovan, E., Ambalavanan, N., et al. Follow-up compliance of newborn intensive care Unit (NICU) survivors. Ped Res 47(4):312A, 2000. (platform presentation)
26. Carlo, W.A., Stark, A.R., Bauer, C., Donovan, E.F., et al. Effects of minimal ventilation in a multicenter randomized controlled trial of ventilator support and early corticosteroid therapy in extremely-low-birth-weight infants. Ped Res 47(4):2310, 2000. (platform presentation)
27. Stark, A.R., Carlo, W.A., Bauer, C.R., Donovan, E.F., et al. Serious complications in a randomized trial of early stress dose dexamethasone (DEX) in extremely low birth weight (ELBW) infants. Ped Res 47(4):434A, 2000. (platform presentation)
28. Warner, B.B., Kiely, J.L., Donovan, E.F.: Multiple births and outcome. In: Clinics in Perinatology, Vohr, B.R. (eds), W.B. Saunders Co., Philadelphia, 27(2), June 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
BARBARA B. WARNER	RESEARCH ASSISTANT PROFESSOR

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Dayton, Dayton, OH	B.S.	1979	Nutrition
University of Massachusetts, Amherst, MA	M.S.	1981	Epidemiology
University of Cincinnati, Cincinnati, OH	M.D.	1985	Medicine
Children's Hospital Medical Center, Cincinnati, OH		1988	Pediatric Residency
Children's Hospital Medical Center, Cincinnati, OH		1991	Neonatology Fellowship
Children's Hospital Medical Center, Cincinnati, OH		1994	Research Scholar

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

ACADEMIC APPOINTMENTS:

Research Instructor, Department of Pediatrics, Division of Pulmonary Biology, Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH -- 07/01/94-08/31/97

Research Assistant Professor, Department of Pediatrics, Division of Pulmonary Biology, Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH -- 09/01/97 to present

MEMBERSHIPS:

American Academy of Pediatrics

PUBLICATIONS:

1. Wispe JR, Clark JC, Warner BB, Fajardo D, Hull WM, Holtzman RB, Whitsett JA: Tumor necrosis factor-alpha inhibits expression of pulmonary surfactant protein. J Clin Invest 86:1954-1960, 1990.
2. Warner BB, Burhans MS, Clark JC, Wispe JR: Tumor necrosis factor increases manganese superoxide dismutase expression in pulmonary adenocarcinoma cells: Protection against oxidant injury. Am J Physiol: Lung Cell Mol Biol 260:L296-L301, 1991.
3. Wispe JR, Warner BB, Clark JC, Dey CR, Neuman J, Glasser SW, Crapo JD, Chang LY, Whitsett JA: Human Mn-superoxide in pulmonary epithelial cells of transgenic mice confers protection from oxygen injury. J Biol Chem 267-23937-23941, 1992.
4. Warner BB, Papes R, Heile M, Wispe JR: Expression of human Mn-SOD in Chinese hamster ovary cells confers protection from oxidant injury. Am J Physiol: Lung Cell Mol Physiol 264:L598-L605, 1993.
5. Warner BB, Stuart L, Gebb S, Wispe JR: Redox regulation of manganese superoxide dismutase. Am J Physiol: Lung Cell Mol Physiol 271(15):L150-L158, 1996.
6. Warner BB, Stuart LA, Papes RA, Wispe JR: Functional and pathological effects of prolonged hyperoxia in neonatal mice. Am J Physiol (Lung Cell Mol Physiol) 275:L110-L117, 1998.

Warner, Barbara B., M.D.

Abstracts:

1. Warner BB, Burhans MS, Wispe JR: Regulation of CuZn superoxide dismutase expression by dexamethasone. Ped Res 25:1969A, 1989.
2. Warner BB, Burhans JS, Wispe JR: Tumor necrosis factor regulates manganese SOD activity in a human pulmonary adenocarcinoma cell line. Pediatric Res 25:1970A, 1989
3. Warner B, Wispe JR: Mechanisms involved in tumor necrosis factor induction of Mn-SOD: modulation of dexamethasone. Am Rev Respir Dis 141:A817, 1990.
4. Warner Burhans MS, Wispe JR: Incresed Mn-SOD protects against oxidative injury. Ped Res 27:1909A, 1990.
5. Warner BB, Rice WR, Wispe JR: Tumor necrosis factor-α induction of Mn-SOD is not mediated by protein kinase C, cyclic nucleotides or Ca^{2+} mobilization. Ped Res 27:1910A, 1990.
6. Warner B, Burhans Ms, Wispe JR: Paraquat increaes expression of surfactant protein A and Mn-SOD in pulmonary adenocarcinoma cells. Ped Res 29:334A, 1991.
7. Warner B, Wispe J, Whitsett J, Mitterender N, Trapnell B: Inflammatory response following adenoviral mediated gene transfer in hamster and rabbit. Pediatr Pulmon Sup 9:246, 1993.
8. Warner B, Stuart L, Wispe J: Tumor necrosis factor increases Mn-SOD expression in redox sensitive process involving NFkB. Am Rev Respir Dis 151:A644, 1995.
9. Warner B, Musial J, Kiely J, Chenier T, Donovan E: Delivery site and very low birth weight outcomes. Ped Res 47(4):328A, 2000.

Book Chapters:

1. Warner BB, Kallapur S: Neonatal neurology in the neonatal nursing education series. Altimer L and Lott J (eds) Observatory Group Inc., Cincinnati, OH, 1989.
2. Warner BB, Wispe JR: Free radical-mediated diseases in pediatrics. In: Clinics in Perinatology. Roberts RJR, ed., Philadelphia: WB Saunders Company. Seminars in Perinatology 16:47-57, 1992.
3. Whitsett JA, Pryhuber GS, Rice WR, Warner BB, Wert SE: Acute Respiratory Disorders. In: Neonatology: Pathophysiology and Management of the Newborn, Fourth Edition, G.B. Avery, M.A. Fletcher and M.G. MacDonald (eds.), J.B. Lippincott Co., Philadelphia, PA, Chapter 29:429-452, 1994.
4. Warner BB, Wispe JR: Gene therapy for the lung. In: Current Topics in Neonatology. Hansen TE and McIntosh N (eds). Philadelphia, WB Saunders, pp 177-194, 1996.
5. Warner BB, Wispe JR: Transgenic models for the study of lung injury and repair: integration of molecular, functional and cellular approaches. In Oxygen, Gene Expression, and Cellular Function. Lung Biology in Health and Disease. Clerch LB and Massaro DJ (eds). New York: Marcel Dekker, pp 139-158, 1997.
6. Warner BB, Kiely JL, Donovan EF: Outcome of the very low birth weight infant. Clin Perinatol 27:347-361, 2000.

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Jean J. Steichen, M.D.	Professor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Nancy Medical School Nancy, France	Surgery, D. Obstet., D.	1965	Medicine, Physiol. Histo- Biochemistry, Pathology
University of Paris Medical School Paris, France	M.D.	1969	Medicine, Surgery, Obstetrics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership o any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during th past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

ACADEMIC
APPOINTMENTS:

Instructor in Pediatrics, University of Cincinnati, July 1972-June 1974; Fels Assistant Professor of Pediatrics University of Cincinnati, July 1974-1977; Assistant Professor of Obstetrics and Gynecology, University of Cincinnati, July 1976-1981; Attending Pediatrician, University Hospital, University of Cincinnati Medical Center, July 1974; Attending Pediatrician/Attending Physician, Newborn Division, Children's Hospital Medical Center, Cincinnati, Ohio, January 1975-; Assistant Professor of Pediatrics, Obstetrics and Gynecology, University of Cincinnati, 1977 1981; Attending Pediatrician/Neonatologist, Jewish Hospital, Cincinnati, Ohio, 1978-present; Associate Professor of Pediatrics Obstetrics and Gynecology, University of Cincinnati, 1981- ; Attending Pediatrician/Neonatologist, Bethesda Hospital Cincinnati, Ohio, 1987-; Director, Infant Follow Up Program, University Hospital/Children's Hospital Medical Center, Cincinnati, Ohio, 1989; Clinical Director, Health Alliance Neonatology, February 1997-; Interim Director, University Hospital NICU and Fullterm Nurseries, May 1997-1998; Director, University Hospital NICU and Fullterm Nurseries, May 1998-; Director, Pediatrics and Neonatal Services, Jewish Hospital, June 1998; Professor of Pediatrics, University of Cincinnati, June 1999

HONORS

1965-1969	Scholarship Award - Department of Education and Health, Luxembourg Government
1972	Research Fellowship Award - National Institute of Health
1983-85	March of Dimes Grant Committee
1984	Visiting Professor, Peking Children's Hospital
1985	Invited Speaker, 91st Ross Conference on Pediatric Research, "Effect of Mode of Feeding Vitamin D Calciu and Phosphorus in Human Milk and the Breast-fed Infant," Boulder, Arizona.
1986	National Institute of Health Ad Hoc Study Section
1989	Invited Speaker. Hamilton County Department of Human Services, "Special Needs and Care of Medically Fragile Infants: Cocaine toxic infants," Cincinnati, Ohio
1991	ESPGAN Summer School, "Bone Mineralization and Mineral Metabolism in Low Birth Weight Infants," Londo
1992	NIH-Neonatal Research Network Developmental Follow-up Consultant Subcommittee, Co-Chair
1995	Advisory Board and Writing Committee for MedImmune
1996	Excellence in Teaching (Presented by Andrea Lindell 5/29/96)
1998	Consultant to the Minister of Public Health in Luxembourg

1. Koo VKK, Kaplan LA, Horn J, Tsang RC, Steichen JJ: Aluminum in parenteral nutrition solution - sources and possibl alternatives. Journal of Parenteral and Enteral Nutrition, Vol. 10:(6)591-595, March, 1986.
2. Steichen JJ: Human Milk: Vitamin D Nutrition and Bone Mineralization in the Term Infant. In Filer LJ Jr, Fomon SJ (eds) Report of the 91st Ross Conference on Pediatric Research, Columbus, OH., p 115-119, 1986.
3. Koo WWK, Tsang RC, Steichen JJ, Succop P, Oestreich A, Farrell M, Noseworthy J, Horn J: Parenteral Nutrition for Infants: II. Effect of High Versus Low Calcium and Phosphorus Content. Journal of Pediatric Gastroenterology and Nutrition, 6:96-104, 1987.
4. Steichen JJ, Krug-Wispe S, Tsang RC: Breastfeeding the low birth weight preterm infant. Clinics in Perinatology Vol 14, (1)143-183, 1987.
5. Steichen JJ, Tsang RC: Bone mineralization and growth in term infants prospectively fed soy-based or cow milk-base formula. Condensed Title: Bone Mineralization in Soy Versus Cow Milk Formula. J. Pediatr, 110:(5)687-692, May, 1987.
6. Koo WWK, Tsang RC, Steichen JJ, Succop P, Oestreich A, Farrell M, Noseworthy J, Horn J: Parenteral Nutrition for Infants: I. Vitamin D Requirement. Condensed title: Vitamin D Requirement in Infants Receiving Parenteral Nutrition. Journal of Parenteral and Enteral Nutrition, Vol. II:(2)172-176, 1987.
7. Mimouni F, Steichen JJ, Tsang RC, Hertzberg V., Miodovnik M: Decreased bone mineral content of infants of diabeti mothers. Am J of Perinatology 5:339-343, 1988.
8. Steichen JJ, Keriakes JG, Tsang RC: Radiation dose to small infants from single-photon absorptiometry. Radiology 1988 168:169-170.
9. Koo WWK, Sherman R, Succop P, Krug-Wispe SK, Oestreich AE, Tsang RC, Steichen JJ: Sequential bone mineral conten in very low birth weight infants with and without fractures and rickets. Journal of Bone and Mineral Research, Vol. 3(2):193-197, 1988.
10. Steichen JJ, Steichen Asch PA, Tsang RC: Bone Mineral Content Measurement in Small Infants by Single Photon Absorptiometry: Current Methodologic Issues. Journal of Pediatrics, Vol. 113, No. 1, part 2, pp 181-187, July 1988
11. Steichen JJ, Tsang RC: Bone Mineralization and Growth in Term Infants and Growth in Term Infants Fed-Soy-Based o Cow Milk-Based Formula. Pediatrics Digest 2:11-13, 1988.
12. Keller D, Steichen JJ: **Blue Chip Baby: The Guide to Having a Baby in Cincinnati.** November 1988, Baker Place Press
13. Koo WWK, Sherman R, Succop P, Krug-Wispe S, Tsang RC, Steichen JJ, Crawford AH, Oestreich AE. Fractures and rickets in very low birth weight infants: conservative management and outcome. Journal of Pediatric Orthopaedics 9:326-330, 1989.
14. Ford LM, Steichen J, Babcock D, O'Grady D, Fogelson MH: Neurologic statue and intracranial hemorrhage (ICH) in ver low birthweight (VLBW) preterm infants: Results at one year and five years. American Journal of Diseases of Childre 43:1186-1190, 1989.
15. Steichen J: Bone mineral densitometry methods in infants. In Klish WJ, Kretchmer N (eds): **Body Composition Measurements in Infants and Children**, Report of the Ninety-Eighth Conference on Pediatric Research, Columbus, Ohio Ross Laboratories, 1989, p.48-53.
16. Ford LM, Han K, Steichen J, Babcock D, Fogelson H: Very low birth weight, preterm infants with or without intracranial hemorrhage: Neurologic, cognitive and cranial MRI correlations at 4-8-year follow-up. Clinical Pediatrics 28(7):302-310, 1989.
17. Koo W, Succop P, Bornschein R, Krug-Wispe S, Steichen J, Tsang R, Berger, OG. Serum Vitamin D Metabolites in Young Children with Chronic Lead Exposure. Pediatrics 87:680-687, 1991.
18. Steichen JJ, Tsang RC: Osteopenia and rickets of prematurity. In R. Polin (ed). **Fetal and Neonatal Physiology,** W. B. Saunders Company, Volume 2 of Chapter 177:1767-1777, 1991.
19. Steichen JJ: Surfactant replacement therapy of respiratory distress syndrome. Bulletinm de la Societe des Sciences Medicales du Grand-Duchel de Luxemburg. 127 #2. p. 59-76, 1990.
20. Steichen JJ, Koo WWK: Bone mineralization and mineral metabolism in term infants. Monatssche Kinderheilkunde, 140[Suppl]: S 21-S 27. Springer-Verlag, 1992.
21. Connor E, Topp F, Steichen J, Gratton T, et al: Reduction of RSV hospitalization among premature infants and infants with bronchopulmonary dysplasia using Respiratory Syncytial Virus Immune Globulin prophylaxis. Pediatrics 99:93-99, 1997.
22. Dr. Thordur Thorkelsson (Steichen JJ, Mentor) Extremely low birth weight infant predictors of developmental outcome and school performance. (In partial fulfillment for the degree of Master of Science, June 1994).
23. Koo WWK, Steichen JJ: Osteopenia and rickets of prematurity. In R. Polin (ed). **Fetal and Neonatal Physiology,** W. B. Saunders Company. Second edition, volume 2, chapter 207, pg. 2335, 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
BETH F. HABERMAN, M.D.	NEONATOLOGY FELLOW

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Indiana University, Bloomington, IN	B.A.	1989	Chemistry
University of Louisville School of Medicine, Louisville, KY	M.D.	1993	Medicine
Children's Hospital Medical Center, Cincinnati, OH			
University of Cincinnati and Children's Hospital Medical		1993-1996	Pediatric Residency
Center, Cincinnati, OH		1996-1999	Neonatology Fellowship

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Academic Appointment:

Assistant Professor of Clinical Pediatrics
Associate Director, Follow-up Research
University of Cincinnati Medical Center and Children's Hospital, Cincinnati, Ohio

Awards and Honors:

Charles B. Atwood Scholarship for Academic Excellence, 1985-89
Indiana University Award for entering Valedictorians, 1985-86
Golden Key National Honor Society, 1988-89
Dean's List, 1985-89
Chemistry Honor Roll, 1988-89
Billy F. Andrews Award for Excellence in Pediatrics, 1993
Alpha Omega Alpha Scholarship Award, 1993
Outstanding Resident in Neonatology, 1996

Professional Organizations:

American Academy of Pediatrics
Kentucky Pediatric Society

Publications and Presentation:

Haberman B, Donovan E, Ambalavanan N, Hansen N, Bohr B, and the NICHD Neonatal Research Network Follow-up Subcommittee. Follow-up compliance of newborn intensive care unit (NICU) survivors. Ped Res 47(4):312A, 2000 (Platform presentation at the Society for Pediatric Research).

Haberman B, Wert S, Whitsett J, Iwamoto H. Effects of Perfluorocarbon in Spontaneously Breathing Mice. [Abstract #700022h] Pediatric Research, 1998.

Dr. Haberman publications and presentations continued

Haberman B, Wert S, Whitsett J, Iwamoto H. Effects of Perfluorocarbon in Spontaneously Breathing Mice. [Abstract, Platform presentation] Pediatric Research, 1998.

Speaker at the Annual Tri-Health Nursing Conference, 1997. Topic: Novel Respiratory Therapies: Nitric Oxide and Liquid Ventilation.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Baha M. Sibai, MD	Professor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
American University, Beirut Lebanon	BS	1968	
American University, Beirut Lebanon	MD	1972	
American University, Beirut Lebanon		1976	Residency
University of Tennessee, Memphis, TN		1980	Fellowship

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Research and Professional Experience:

1977-78 **Instructor**, Department of OB/GYN,University of Texas Southwestern Medical School, Dallas, TX.
1978-80 **Instructor**, Division of Maternal-Fetal Medicine, Department of OB/GYN, University of Tennessee, Memphis, TN
1980-82 **Assistant Professor**, Division of Maternal-Fetal Medicine, Department of OB/GYN, University of Tennessee, Memphis, TN
1982-87 **Associate Professor**, Division of Maternal-Fetal Medicine, Department of OB/GYN, University of Tennessee, Memphis, TN
1986-2000 **Director**, Maternal-Fetal Medicine Fellowship, Dept. of OB/GYN, University of Tennessee, Memphis, TN
1987-2000 **Professor**, Division of Maternal-Fetal Medicine, Dept. of OB/GYN, University of Tennessee, Memphis, TN
1989-2000 **Chief**, Division of Maternal-Fetal MedicineDepartment of OB/GYN, University of Tennessee, Memphis, TN
2000-pres **Professor** and **Chairman,** Department of OB/GYN, University of Cincinnati College of Medicine,Cincinnati, OH

Publications:

10. Sibai BM, Gordon T, Thom E, Caritis SN, Klebanoff M, McNellis D, Paul RH, and the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units: Risk factors for preeclampsia in healthy nulliparous women: A prospective multicenter study. Am J Obstet Gynecol 1995;172(2pt1):642-8.
11. Sibai BM, Caritis SN, Thom E, Shaw K, McNellis D, and the NICHD MFM Network: Low-dose aspirin in nulliparous women: Safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. Am J Obstet Gynecol 1995;172(5):1553-6.
12. Friedman SA, Schiff E, Kao L, Sibai BM: Neonatal outcome after preterm delivery for preeclampsia. Am J Obstet Gynecol 1995;172(6):1785-8.
13. Chari RS, Friedman SA, O'Brien JM, Sibai BM: Daily antenatal testing in women with severe preeclampsia. Am J Obstet Gynecol 1995;173(4):1207-11.
14. Lewis R, O'Brien JM, Ray DT, Sibai BM: The impact of initiating a human immunodeficiency virus screening program in an urban obstetric population. Am J Obstet Gynecol 1995;173(4):1329-33.
15. Chari RS, Friedman SA, Schiff E, Frangieh AY, Sibai BM: Is fetal neurologic and physical development accelerated in preeclampsia? Am J Obstet Gynecol 1996;174:829-832.
16. Schiff E, Friedman SA, Sibai BM, Maschiach S, Hart O, Barkai G: Maternal and neonatal outcome of 846 term singleton breech deliveries: Seven-year experience at a single center. Am J Obstet Gynecol 1996;175:18-23.
17. Sibai BM: Drug Therapy: Treatment of hypertension in pregnant women. *Drug Therapy Series* , N Engl J Med 1996;335(4):257-65.

18. Briggs R, Chari RS, Mercer B, Sibai B: Postoperative incision complications following cesarean section in patients with antepartum syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP): Does delayed primary closure make a difference? Am J Obstet Gynecol 1996;175(1[pt4]):893-6.
19. Egerman RS, Witlin AG, Friedman SA, Sibai BM: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in pregnancy: Review of 11 cases. Am J Obstet Gynecol 1996;175(1[pt4]):950-6.
20. Schucker JL, Mercer BM, Audibert F, Lewis RL, Friedman SA, Sibai BM: Serial amniotic fluid index in severe preeclampsia: A poor predictor of adverse outcome. Am J Obstet Gynecol 1996;175(1[pt4]):1018-23.
21. Schiff E, Friedman SA, Stampfer M, Kao L, Barrett PH, Sibai BM: Dietary consumption and plasma concentrations of vitamin E in pregnancies complicated by preeclampsia. Am J Obstet Gynecol 1996;175(1[pt4]):1024-8.
22. Copper RL and the National Institute of Health/Maternal-Fetal Medicine Units Network (Sibai BM): The preterm prediction study: Maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. Am J Obstet Gynecol 1996;175(1[pt5]):1286-92.
23. Schiff E, Friedman SA, Kao L, Sibai BM: The importance of urinary protein excretion during conservative management of severe preeclampsia. Am J Obstet Gynecol 1996;175(1[pt5]):1313-6.
24. Witlin AG, Mercer BM, Sibai BM: Septic pelvic thrombophlebitis or refractory postpartum fever of undetermined etiology. J Mat Fet Med 1996;5(6):355-8.
25. Egerman RS, Pierce WF IV, Andersen RN, Umstot ES, Carr TL, Sibai BM: A comparison of the bioavailability between oral and intramuscular dexamethasone in women in late pregnancy. Obstet Gynecol 1997;89(2):276-80.
26. Witlin AG, Mabie WC, Sibai BM: Peripartum cardiomyopathy: An ominous diagnosis. Orig: Am J Obstet Gynecol 1997;176(1):182-8.
27. Lewis R, Sibai B: Recent advances in the management of preeclampsia. J Mat Fet Med 1997;6(1):6-15.
28. Witlin AG, Friedman SA, Sibai BM: The effect of magnesium sulfate therapy on the duration of labor in women with mild preeclampsia at term: A randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 1997;176(3):623-7.
29. Witlin AG, Mabie WC, Sibai BM: Pregnancy complicated by appendicitis. J Matern Fetal Invest 1997;6(4):190-4.
30. Levine RJ, et al for the National Institute of Health/Maternal-Fetal Medicine Units Network (Sibai BM): Trial of calcium for preeclampsia prevention (CPEP): Rationale, design, and methods. Control Clin Trials 1997;17(5):442-69.
31. Lubarsky SL, Ahokas R, Friedman SA,Sibai BM: The effect of chronic nitric oxide synthesis inhibition on blood pressure and angiotensin II responsiveness in the pregnant rat. Am J Obstet Gynecol 1997;176(5):1069-79.
32. Witlin AG, Friedman SA, Egerman RS, Frangieh AY, Sibai BM: Cerebrovascular disorders complicating pregnancy—beyond eclampsia. Am J Obstet Gynecol 1997;176(6):1139-48.
33. Friedman SA, Schiff EY, Kao L, Kuint J, Sibai BM: Do twins mature earlier than singletons? Results from a matched cohort study. Am J Obstet Gynecol 1997;176(6):1193-1199.
34. Barton JR, Bergauer NK, Jacques DL, Coleman SK, Stanziano GJ, Sibai BM: Does advanced maternal age affect pregnancy outcome in women with mild hypertension remote from term? Am J Obstet Gynecol 1997;176(6):1236-1243.
35. Levine RJ, Hauth JC, Curet LB, Sibai BM, Catalano PM, Morris CD, and the Maternal-Fetal Medicine Units Network: Trial of calcium for prevention of preeclampsia. N Engl J Med 1997;337(2):69-76.
36. Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Meis PJ, Das A, and the Maternal-Fetal Medicine Units Network (Sibai BM): The preterm prediction study: Patterns of cervicovaginal fetal fibronectin as predictors of spontaneous preterm delivery. Am J Obstet Gynecol 1997;177(1):8-12.
37. Lewis RL, Mabie WC, Burlew B, Sibai BM: A biventricular assist device as a bridge to cardiac transplantation in the treatment of peripartum cardiomyopathy. S Med J 1997;90(9):955-8.
38. Mercer BM for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (Sibai BM): Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. JAMA 1997;278(12):989-95.
39. Mabie WC, Barton JR, Sibai BM: Septic shock in pregnancy. Obstet Gynecol 1997;90(4pt1):953-61.
40. Barton JR, Mercer BM, Sibai BM: The effect of nifedipine on urinary excretion of calcium in preeclampsia. Am J Perinatol 1997;14(10):611-14.
41. Egerman RS, Walker RA, Mercer BM, Doss JL, Sibai BM, Andersen RA: Comparison between oral and intramuscular dexamethasone in suppressing unconjugated estriol levels during the third trimester. Am J Obstet Gynecol 1998;179(5):1234-1236.
42. Sibai BM: Prevention of preeclampsia: A big disappointment! Clinical Opinion. Am J Obstet Gynecol 1998;179(5):1275-1278.
43. Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
JON HILMAR FRIDRIKSSON	ASSISTANT PROFESSOR OF CLINICAL PEDIATRICS

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Menntaskolinn i Reykjavik, Reykjavik, Iceland	B.A.	1978-1982	
University of Iceland Medical School, Reykjavik, Iceland	M.D.	1982-1988	Medicine
National University Hospital of Iceland		1988-1991	Residency Program Rotations
Reykjavik City Hospital, Reykjavik, Iceland		1989-1990	Internship Program Rotations
Children's Hospital, Cincinnati, Ohio		1991-1992	Pediatric Internship
Children's Hospital, Cincinnati, Ohio		1992-1994	Pediatric Residency
Children's Hospital & University of Cincinnati, Ohio		1994-1997	Neonatal Fellowship
Hospital for Sick Children, Toronto, Ontario, Canada		1997-1998	Critical Care Medicine Fellow

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Academic Appointment:

8/10/98 - present Assistant Professor of Clinical Pediatrics, Division of Neonatology, Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio

5/1999 -present Nursery Director of Mercy Hospital Anderson, Cincinnati, Ohio

Professional Societies:

American Academy of Pediatrics
Society of Critical Care Medicine
Iceland Medical Association
Reykjavik Medical Association
Association of Junior Medical Doctors in Iceland

Awards:

The Edward Lowe, M.D. Award
Outstanding Senior Resident In Critical Care Medicine 1993-1994
Children's Hospital Medical Center, Cincinnati, Ohio

Publications and Presentations:

Fridriksson JH, Ornar DO. Medferd thunglyndis, stutt Yfirlit. (Treatment of Depression. Brief review). Loeknanemin 1989. Journal of Icelandic Medical Student Association 42:40-44, 1989.

Fridriksson JH. High-frequency ventilation. Lecture. The Seventh Annual Regional Perinatal Nursing and Women's Health Conference, Cincinnati, Ohio, March 1996.

Publications and Presentations continued . . .

Fridriksson JH, Ritschel WA, Iwamoto HS. The effects of nephrectomy on insulin-like growth factor binding protein 4 in fetal sheep. Poster Presentation, Pediatric Societies' Annual Meeting, Washington, D.C., May 1996.

Fridriksson JH, Ritschel WA, Iwamoto HS. The effects of nephrectomy on insulin-like growth factor binding protein 4 in fetal sheep. Oral presentation. Developmental Aspects of Fluid and Electrolyte Homeostasis. Aspen, Colorado, June 1996.

Fridriksson JH, Helmrath MA, Wessel JJ, Warner BW. Hypercalcemia associated with ECLS in neonates. Poster Presentation. The 13th Annual Children's National Medical Center Symposium. Keystone, Colorado, March 1997.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.

Photocopy this page or follow this format for each person

NAME	POSITION TITLE
Jobe, Alan H., M.D., Ph.D.	**Professor of Pediatrics**

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Stanford University, Stanford, CA	B.A.	1967	Biology
Univ. of California, San Diego, CA	M.D.	1973	Medicine
Univ. of California, San Diego, CA	PhD	1973	Cell Biology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

PROFESSIONAL APPOINTMENTS

1973-1975 Pediatric Intern & Resident, University Hospital, UCSD
1975-1977 Neonatology Fellow, University Hospital, UCSD
1977-1977 Assistant Professor, Associate Professor and Professor of Pediatrics, Harbor-UCLA Medical Center
1995-1997 Joseph W. St. Geme, Jr. Professor of Pediatrics - UCLA School of Medicine
1997-Present Professor of Pediatrics, Univ. of Cincinnati, Children's Hospital Medical Center, Cincinnati, OH

SOCIETIES:
Human Embryology and Development Study Section, 7/83-6/87
Chairman, Pediatrics Assembly of American Thoracic Society, 1987
President, Society for Pediatric Research, 1990
Chairman of Steering Committee for NICHD Neonatal Network, 1996 - Present
Member – American Board of Pediatrics – Neonatal Section, 1999 - Present

AWARDS:
Research Career Development Award, NICHD, 1983
E. Mead Johnson Research Award, American Academy of Pediatrics, 1986

PUBLICATIONS: (Selected Reviewed Publications Since 1997)

1. Clark, J.C., Weaver, T.E., Iwamoto, H.S., Ikegami, M., Jobe, A.H., Hull, W.M., Whitsett, J.A.: Decreased lung compliance and air trapping in heterozygous SP-B deficient mice. Am. J. Respir. Cell Mol. Biol. 16:46-52, 1997.
2. Korfhagen, T.R., Bruno, M.D., Ross, G.F., Huelsman, K.A., Ikegami, M., Jobe, A.H., Wert, S.E., Stripp, B.R., Morris, R.E., Glasser, S.W., Bachurski, C.J., Iwamoto, H.S., Whitsett, J.A.: Preservation of lung function and deficiency of tubular myelin in SP-A gene targeted mice. Proc. Natl. Acad. Sci. (USA) 93:9594-9599, 1996.
3. Polk, D.H., Ikegami, M., Jobe, A.H., Sly, P., Kohan, R., Newnham, J.: Preterm lung function following retreatment with antenatal betamethasone in preterm lambs. Am. J. Obstet. Gynecol. 176:308-315, 1997.
4. Ikegami, M., Korfhagen, T.R., Bruno, M.D., Whitsett, J.A., Jobe, A.H.: Surfactant metabolism in surfactant protein A deficient mice. Am. J. Physiol. 272:L479-485, 1997.
5. Henry, M.D., Ikegami, M., Jobe, A.H.: Testing surfactant treatment responses: a comparison of two models. Biol. Neonate 71:181-189, 1997.
6. Tokieda, K., Whitsett, J.A., Clark, J.C., Weaver, T.E., Ikeda, K., McConnell, K.B., Jobe, A.H., Ikegami, M., Iwamoto, H.S.: Pulmonary dysfunction in neonatal SP-B deficient mice. Am. J. Physiol. 273:L875-L882, 1997
7. Rebello, C.M., Ikegami, M., Hernandez, R.E., Jobe, A.H.: Surfactant protein-B and lung function in surfactant treated preterm lambs. Biol. Neonate 71:327-336, 1997.
8. Rebello, C.M., Ikegami, M., Ervin, M.G., Polk, D.H., Jobe, A.H.: Postnatal lung function and protein permeability after fetal or maternal corticosteroids in preterm lambs. J. Appl. Physiol. 83:213-218, 1997
9. Akinbi, H.T., Breslin, J.S., Ikegami, M., Iwamoto, H.S., Clark, J.C., Whitsett, J.A., Jobe, A.H., Weaver, T.E.: Rescue of SP-B knockout mice with a truncated SP-B proprotein: function of the C-terminal propeptide. J. Biol. Chem. 272:9640-9647, 1997.
10. Ikegami, M., Jobe, A.H., Newnham, J., Polk, D.H., Willet, K.E., Sly, P.: Repetitive prenatal glucocorticoids affect lung function and growth in preterm lambs. Am. J. Respir. Crit. Care Med. 156:178-184, 1997
11. Pinkerton, K.E., Willet, K.E., Peake, J.L., Sly, P.D., Jobe, A.H., Ikegami, M.: Prenatal glucocorticoid and T_4 effects on lung morphology in preterm lambs. Am. J. Respir. Crit. Care Med. 156:624-630, 1997
12. Ikegami, M., Jobe, A.H., Reed Huffman, J.A., Whitsett, J.A.: Surfactant metabolic consequences of overexpression of GM-CSF in type II cells of GM-CSF deficient mice. Am. J. Physiol. 273:L709-L714, 1997
13. Berry, L.M., Polk, D.H., Ikegami, M., Jobe, A.H., Padbury, J.F., and Ervin, M.G.: Preterm newborn lamb renal and cardiovascular responses after fetal or maternal antenatal betamethasone. Am. J. Physiol. 272:R1972-R1979, 1997

14. Jobe, A.H., Ikegami, M., Padbury, J., Polk, D.H., Gonzales, L.W., Ballard, P.L.: Combined effects of fetal B-agonist stimulation and glucocorticoids on lung function of preterm lambs. Biology Neonate, 72:305-313, 1997.
15. Wada, K., Jobe, A.H., Ikegami, M.: Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. J. Appl. Physiol., 83:1054-1061, 1997.
16. Ballard, P.L., Ning, Y., Polk, D., Ikegami, M., Jobe, A.H.: Glucocorticoid regulation of surfactant components in immature lambs. Am. J. Physiol., 273:L1048-L1057, 1997.
17. Ikegami, M., Wada, K., Emerson, G.A., Rebello, C.M., Hernandez, R.E., Jobe, A.H.: Effects of ventilation style on surfactant metabolism and treatment response in preterm lambs. Am. J. Respir. Crit. Care Med., 157:638-644, 1998.
18. Emerson, G.A., Bry, K., Hallman, M., Jobe, A.H., Wada, N., Ervin, M.G., Ikegami, M.: Intra- amniotic interleukin-1a treatment alters postnatal adaptation in premature lambs. Biology Neonate, 72:370-379, 1997.
19. Willet, K.E., Jobe, A.H., Ikegami, M., Polk, D., Newnham, J., Kohan, R., Gurrin, L. & D. Sly, P.D. Postnatal lung function after prenatal steroid treatment in sheep: Effect of gender. Pediatr. Res., 42:885-892, 1997
20. Davis, A.J., Jobe, A.H., Häfner, D., and Ikegami, M. Lung function in premature lambs and rabbits treated with a recombinant SP-C surfactant. Am. J. Respir. Crit. Care Med., 157:553-559, 1998.
21. Jobe, A.H., Wada, N., Berry, L.M., Ikegami, M., and Ervin, M.G.: Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. Am. J. Obstet. Gynecol., 178:880-885, 1998
22. Ikegami, M., Korfhagen, T.R., Whitsett, J.A., Bruno, M.D., Wert, S.E., Wada, K., and Jobe, A.H.: Characteristics of surfactant from SP-A deficient mice. Am. J. Physiol., 275:L245-L254, 1998.
23. Ervin, M.G., Seidner, S.T., Leland, M.M., Ikegami, M., Jobe, A.H.: Direct fetal glucocorticoid treatment alters postnatal adaptation in premature newborn baboons. Am. J. Physiol., 274:R1169-R1176, 1998.
24. Ikegami, M., Horowitz, A.D., Whitsett, J.A., and Jobe, A.H.: Clearance of SP-C and recombinant SP-C in vivo and in vitro. Am. J. Physiol., 274:L933-L939, 1998.
25. Jobe, A.H.: Surfactant homeostasis in corticotropin-releasing hormone deficient mice. Am. J. Respir. Crit. Care Med., 158:840-845, 1998.
26. Jobe, A.H., Newnham, J., Willet, K., Sly, P. and Ikegami, M.: Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. Pediatrics, 102:1116-1125, 1998.
27. Walther, F.J., Jobe, A.H. and Ikegami, M.: Repetitive prenatal glucocorticoid therapy reduces oxidative stress in the lungs of preterm lambs. J. Appl. Physiol., 85:273-278, 1998.
28. Korfhagen, T.R., Sheftelyevich, V., Burnhans, M.S., Bruno, M.D., Ross, G.F., Wert, S.E., Stahlman, M.T., Jobe, A.H., Ikegami, M., Whitsett, J.A. and Fisher, J.H.: Surfactant Protein-D regulates surfactant phospholipid homeostasis in vivo. J. Biol. Chem., 273:28438-28443, 1998.
29. Seidner, S.R., Jobe, A.H., Coalson, J.J., and Ikegami, M.: Abnormal surfactant metabolism and function in preterm ventilated baboons. Am. J. Respir. Crit. Care Med.,158:1982-1989, 1998.
30. Ikegami, M., and Jobe, A.H. Surfactant Protein-C in ventilated lamb lung. Pediatr. Res. 44:860-864, 1998.
31. Willet, K.E., McMenamin, P., Pinkerton, K.E., Ikegami, M., Jobe, A.H., Gurrin, L., and Sly, P. Lung morphometry and collagen and elastin content: Changes during normal development and following prenatal hormones in sheep. Pediatr. Res. 45:615-625, 1999.
32. Newnham, J.P., Evans, S.F., Godfrey, M., Huang, W., Ikegami, M., and Jobe, A.H.: Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J. Maternal-Fetal Medicine, J. Matern. Fetal Med. 8:81-87, 1999.
33. Reed, J.A., Ikegami, M., Cianciolo, E.R., Lu, W., Cho, P.S., Hull, W., Jobe, A.H. and Whitsett, J.A.: Aerosolized GM-CSF ameliorates pulmonary alveolar proteinosis. Am. J. Physiol. 276:L556-L563, 1999.
34. Michna, J., Jobe, A.H., and Ikegami, M. Positive end expiratory pressure preserves surfactant function in preterm lambs. Am. J. Respir. Crit. Care Med. 160:634-639, 1999.
35. Ikegami, M., Harrod, K.S., Whitsett, J.A., and Jobe, A.H. CCSP deficiency does not alter surfactant homeostasis during adenoviral infection. Am. J. Physiol. 277:L983-L987, 1999.
36. Tan, R.C., Ikegami, M., Jobe, A.H., Yao, L., Possmayer, F., and Ballard, P.: Developmental and glucocorticoid regulation of surfactant protein mRNAs in preterm lambs. Am. J. physiol. 277:L1142-L1148, 1999.
37. Ross, G.F., Ikegami, M., Steinhilber, W., and Jobe, A.H. Surfactant protein C in fetal and ventilated preterm rabbit lungs. Am. J. Physiol. 277:L1104-L1108, 1999.
38 Bunt, J.E., Carnielli, V.P., Seidner, S., Ikegami, M., Wattimena, J.L.D., Sauer, P.J.J., Jobe, A.H., and Zimmerman, L.J.I.: Metabolism of endogenous surfactant in premature baboons and effect of prenatal corticosteroids. Am. J. Respir. Crit Care Med. 160:1481-1485, 1999.
39. Rider, E.D., Ikegami, M., Pinkerton, K., Peake, J.L., and Jobe, A.H.: Lysosomes from rabbit type II cells catabolize surfactant lipids. Am. J. Physiol. 278:L68-L74, 2000.
40. Ikegami, M., Whitsett, J.A., Chroneos, Z.C., Ross, G.F., Reed, J.A., Bachurski, C.J., and Jobe, A.H.: IL-4 increases surfactant and regulates metabolism in vivo. Am. J. Physiol./Lung Cell & Mol Physiol. 278:L75-L80, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Heubi, James E.	Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Indiana University, Bloomington, Indiana	A.B.	1970	Zoology
Indiana University, Indianapolis, Indiana	M.D.	1973	Medicine
Honors: Phi Eta Sigma (1967); Alpha Epsilon Delta (1967); Phi Beta Kappa (1970); Alpha Omega Alpha (1973)			

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Academic Appointments

1974-75	Residency, Pediatrics, James Whitcomb Riley Hospital for Children, Indianapolis, IN
1975-78	Fellow, Pediatric Gastroenterology, Children's Hospital Medical Center, Cincinnati, OH
1978-79	Research Scholar, Division of Pediatric Gastroenterology, Cincinnati Children's Hospital
1979-83	Assistant Professor of Pediatrics, University of Cincinnati
1983-89	Associate Professor of Pediatrics, University of Cincinnati
1989-pres.	Professor of Pediatrics, University of Cincinnati

Professional Appointments

1982-88	Assistant Director, General Clinical Research Center, Cincinnati Children's Hospital, OH
1988-pres.	Director, General Clinical Research Center, Cincinnati Children's Hospital, OH
1997-pres.	Member, GCRC Review Committee, National Center for Research Resources, NIH

Publications (Selected from 110 total)

1. Heubi JE, Tsang RC, Steichen JJ, Chan GM, Chen I-W, DeLuca HF: 1,25-dihydroxyvitamin D_3 in childhood hepatic osteodystrophy. J Pediatr 94:977-82, 1979.
2. Heubi JE, Balistreri WF, Suchy FJ, et al: Enterohepatic circulation of bile acids in infants and children with ileal resection. J Lab Clin Med 95:231-40, 1980.
3. Heubi JE, Balistreri W, Suchy FJ: Bile salt metabolism in the first year of life. J Lab Clin Med 100:127-36, 1982.
4. Heubi JE, Balistreri WF, Fondacaro JD, Partin JC, Schubert WK: Primary bile acid malabsorption: Defective in vitro ileal active bile acid transport. Gastroenterology 83:804-11, 1982.
5. Heubi JE, Soloway RD, Balistreri WF: Biliary lipid composition in healthy and diseased infants, children and young adults. Gastroenterology 82:1295-9, 1982.
6. Heubi JE, Burstein S, Sperling MA, et al: The role of human growth hormone in the regulation of cholesterol and bile acid metabolism. J Clin Endocrinol Metab 57:885-91, 1983.
7. Sokol RJ, Farrell MK, Heubi JE, Tsang RC, Balistreri WF: Comparison of vitamin E and 25-hydroxyvitamin D absorption during childhood cholestasis. J Pediatr 103:712-7, 1983.
8. Sokol RJ, Heubi JE, Iannaccone ST, et al: Vitamin E deficiency with normal serum vitamin E concentrations in children with chronic cholestasis. N Engl J Med 310:1209-12, 1984.

9. Setchell KDR, Suchy FJ, Welsh MB, Zimmer-Nechemias L, Heubi J, Balistreri WF: Delta^4-3-oxosteroid 5 beta-reductase deficiency described in identical twins with neonatal hepatitis - A new inborn error in bile acid synthesis. J Clin Invest 82:2148-57, 1988.
10. Munoz SJ, Heubi JE, et al.: Vitamin E deficiency in primary biliary cirrhosis. Hepatol, 9:525-31, 1989.
11. Heubi JE, Hollis BW, Tsang RC: Bone disease in chronic childhood cholestasis, II. Better absorption of 25-OH vitamin D than vitamin D in extrahepatic biliary atresia. Pediatr Res 27:26-31, 1990.
12. Heubi JE, O'Connell NC, Setchell KDR: Ileal resection/dysfunction in childhood predisposes to lithogenic bile only after puberty. Gastroenterology, 103:636-640, 1992.
13. Argao E, Heubi J, et al.: D-a-tocopheryl polyethylene glycol-1000 succinate enhances the absorption of vitamin D in cholestatic liver disease of infancy and childhood. Pediatr Res 31:146-150, 1992.
14. Sokol RJ, Butler-Simon N, Conner C, Heubi JE, et al.: Multi-center trial of D-alpha tocopheryl polyethylene glycol-1000 succinate for treatment of vitamin E deficiency in children with chronic cholestatic liver disease. Gastroenterology 104: 1727-1735, 1993.
15. Argao EA, Balistreri WF, Hollis BW, Ryckman FC, Heubi JE: Effect of orthotopic liver transplantation on bone mineral content and serum vitamin D metabolites in infants and children with chronic cholestasis. Hepatology 20:598-603, 1994.
16. Higgins JV, Dumaswala R, Paul J, Heubi JE: Down-regulation of taurocholate transport by the ileal BBM and liver BLM in biliary diverted rats. Am J Phys 267:G501-7, 1994.
17. Dumaswala R, Berkowitz D, Setchell KDR, Heubi JE: Effect of fasting on the enterohepatic circulation of bile acids in rats. Am J Physiol 267:G836-42, 1994.
18. Heubi JE: Pediatric Hepatobiliary Disease. Current Opinion in Gastroenterology 11:463-466, 1995.
19. Dumaswala R, Berkowitz D, Heubi JE: Adaptive response of the enterohepatic circulation of bile acids in extrahepatic cholestasis. Hepatology 23:623-629, 1996.
20. Kalkwarf HJ, Specker BL, Heubi JE, Vieira NE, Yergey AL: Intestinal calcium absorption of women during lactation and after weaning. Am J Clin Nutr 63:526-31, 1996.
21. Heubi JE: Liver and Biliary System. In: Essentials of Physiology, 2nd ed. Sperelakis N, Banks RO, eds, Little, Brown and Co., New York, pp. 511-8, 1996.
22. Oelkers P, Kirby LC, Heubi JE, et al.: Primary bile acid malabsorption caused by mutations in the ileal sodium-dependent bile acid transporter gene (SLC10A2). J Clin Invest 99(8):1880-7, 1997.
23. Setchell KDR, Zimmer-Nechemias L, Cai J, Heubi JE: Exposure of infants to phytoestrogens from soy-based infant formula. Lancet 350:23-27, 1997.
24. Guo SS, Wisemandle WA, Tyleshevski FE, Roche AF, Chumlea WC, Siervogel RM, Specker B, Heubi J. Inter-machine and inter-method differences in body composition measures from dual energy x-ray absorptiometry and hydrodensitrometry. Age and Nutrition 8: 12-21, 1997.
25. Dellert SF, Nowicki MJ, Farrell MK, Delente J, Heubi JE: The ^{13}C-xylose breath test for the diagnosis of small bowel bacterial overgrowth in children. J Ped Gastroenterol Nutr 25:153-8, 1997.
26. Nowicki MJ, Shneider B, Paul JM, Heubi JE: Glucocorticoids up-regulate taurocholate transport by the ileal brush border membrane. Am J Physiol 273:G197-203, 1997.
27. Heubi JE, Higgins JV, Argao EA, et al: The role of magnesium in the pathogenesis of bone disease in childhood cholestatic liver disease: A preliminary report. J Ped Gastroent Nutr 25:301-6, 1997.
28. Dellert SF, Farrell MK, Specker BL, Heubi JE: Metabolic bone disease in children with short bowel syndrome. J Pediatr 132:516-9, 1998.
29. Sayad AE, Farah RA, Rogers ZR, Heubi JE, et al: Correlation of serum cholylglycine level with hepatic dysfunction in children with sickle cell anemia. Clin Pediatr 38(5):293-6, 1999.
30. Setchell KDR, O'Connell NC, Squires RH, Heubi JE: Congenital defects in bile acid synthesis cause a spectrum of diseases manifest as severe cholestasis, neurologic disease, and fat-soluble vitamin malabsorption. In: Bile Acids in Hepatobiliary Disease. Reyes HB, Leuscher U, Arias IM (eds), Kluwer Academic, Dordrecht, pp. 55-63, 1999.
31. Bove KE, Daugherty CC, Tyson W, Mierau G, Heubi JE, Balistreri WF, Setchell KDR: Perspectives in Pediatric Pathology: Bile acid synthetic defects and liver disease. Pediatr Dev Pathol 3:1-16, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Tariq A. Siddiqi, M.D.	Professor of Obstetrics and Gynecology

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Government College, Lahore, Pakistan	F.Sc.	1969	
King Edward Medical College, Lahore, Pakistan	M.B., B.S.	1975	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

A) Positions:

1981-1983 Instructor, Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
1983-1988 Assistant Professor of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
1984-present Director, Ultrasound Division, Department of Obstetrics and Gynecology, University of Cincinnati, Ohio
1984-present Assistant Professor of Pediatrics, University of Cincinnati, Cincinnati, Ohio
1988-1992 Associate Professor of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
1988-present Director, Maternal-Fetal Medicine, Dept. of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
1990-present Associate Professor of Pediatrics, University of Cincinnati, Cincinnati, Ohio
1992-present Professor of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, Ohio
1995-1999 Director, Department of Obstetrics and Gynecology, The Christ Hospital, Cincinnati, Ohio

B) Professional Education:

1981-1983 Fellowship in Maternal-Fetal Medicine, University of Cincinnati, Dept. of Obstetrics and Gynecology, Cincinnati, OH
1977-1981 Residency, Obstetrics and Gynecology, St. Agnes Hospital, Baltimore, Maryland

C) Honors:

American Academy of Family Physicians (1984, 1987, 1988, 1989, 1990, 1991)
The American College of Nutrition Pediatric Award (1987
Who's Who in the Midwest (1986)
Who's Who in America (1988)
Who's Who in Science and Engineering (1995)
Best Doctors in America (1998,1999)

D) Publications:

1. Mohan R, Irion G, **Siddiqi TA**, Clark KE. Maternal and fetal cardiovascular responses of the normotensive and hypertensive pregnant sheep to parenteral labetalol. Clinical and experimental hypertension, Part B-Hypertension in Pregnancy. B9(3), 1990.
2. Rosenn B, Miodovnik M, Mimouni F, Khoury JC, **Siddiqi TA**. Patient experience in a diabetic program project improves subsequent pregnancy outcome. Obstet Gynecol 77(1):87-91, 1991
3. **Siddiqi T**, Rosenn B, Mimouni F, Khoury J, Miodovnik M. Hypertension during pregnancy in insulin-dependent diabetic women. Obstet Gynecol 77(4):514-15, 1991.
4. Dungy LJ, **Siddiqi TA**, Khan S. C-*jun* and *jun*-B oncogene expression during placental development. Am J Obstet Gynecol 165(6)(1):1853-56, 1991.
5. Mostello D, Hoechstetter L, Bendon RW, Dignan PSJ, Oestreich AE, **Siddiqi TA**. Prenatal diagnosis of the Larsen syndrome: Further definition of a lethal variant. Prenatal Diagnosis 11:215-25, 1991.
6. Rosenn B, Miodovnik M, Combs CA, Khoury J, **Siddiqi TA**. Preconception management of insulin-dependent diabetes: Improvement of pregnancy outcome. Obstet Gynecol 77:846-9, 1991.
7. **Siddiqi TA**, O'Brien Jr. WD, Meyer RA, Sullivan JM, Miodovnik M. *In-Situ* exposimetry: The ovarian ultrasound examination. Ultrasound Med Biod 17(3):257-263, 1991.
8. Jacobson RL, Perez A, Meyer RA, Miodovnik M, **Siddiqi TA**. Prenatal diagnosis of fetal left ventricular aneurysm: A case report and review. Obstet Gynecol 78(3):525-7, 1991.

9. Rosenn B, Miodovnik M, Combs CA, Williams T, Wittekind C, **Siddiqi TA.** Human versus animal insulin in the management of insulin-dependent diabetes: Lack of effect on fetal growth. Obstet Gynecol 78(4):590-3, 1991.
10. Dungy LJ, **Siddiqi TA**, Khan S. Transforming growth factor-β_1 expression during placental development. Am J Obstet Gynecol 165(4):853-7, 1991.
11. Jacobson RL, Brewer A, Eis A, **Siddiqi TA**, Myatt L. Transfer of aspirin across the perfused human placental cotyledon. Am J Obstet Gynecol 165(4):9390944, 1991.
12. Mostello D, Chalk C, Khoury J, Mack CE, **Siddiqi TA**, Clark KE: Chronic anemia in pregnant ewes: Maternal and fetal effects. Am J Physiol. 261 (Regulatory Integrative Comp Physiol 30:R1075-R1083, 1991.
13. Jacobson RL, Dignan P, Miodovnik M, **Siddiqi TA.** Antley-Bixler syndrome. J Ultrasound Med 11:161-164, 1992.
14. Mimouni F, Miodovnik M, Rosenn B, Khoury J, **Siddiqi TA.** Birth trauma in insulin-dependent diabetic pregnancies. Am J Perinatol 9(3):205-208, 1992.
15. **Siddiqi TA**, Review included with publication of Stern JJ, Coulam CB: Mechanism of recurrent spontaneous abortion: Ultrasonographic findings. Am J Obstet Gynecol 166(6):Pt1:1844-1852, 1992.
16. **Siddiqi TA**, Bendon R, Schultz DM, Miodovnik M. Umbilical artery aneurysm: Prenatal diagnosis and management. Obstet Gynecol 80(3,2):530-533,1992.
17. **Siddiqi TA**, O'Brien Jr. WD, Meyer RA, Sullivan JM, Miodovnik M. Human *in-situ* dosimetry: Differential insertion loss during passage through abdominal wall and myometrium. Ultrasound Med Biol 18(8):681-9, 1992
18. Combs CA, Jaekle RK, Rosenn B, Pope M, Miodovnik M, **Siddiqi TA.** Sonographic estimation of fetal weight based on a model of fetal volume. Obstet Gynecol 82(3):365-70, 1993.
19. Rosenn B, Miodovnik M, Combs CA, Khoury J, **Siddiqi TA.** Poor glycemic control and antepartum obstetric complications in women with insulin-dependent diabetes. J Gynecol Obstet 43:21-28, 1993.
20. **Siddiqi TA**, Meyer RA, Korfhagen J, Khoury JC, Rosenn B, Miodovnik M. A longitudinal study describing confidence limits of normal fetal cardiac, thoracic and pulmonary dimensions from 20-40 weeks gestation. J Ultrasound in Med 12(12):731-36, 1993.
21. Mandsager NT, Bendon R, Mostello D, Rosenn B, Miodovnik M, **Siddiqi TA.** Maternal floor infarction: Prenatal diagnosis and clinical significance. Obstet Gynecol 83(5)(1):750-54, 1994.
22. Jaekle RK, Lutz PD, Rosenn B, **Siddiqi TA**, Myatt L. Nitric oxide in metabolites and preterm pregnancy complications. Am J Obstet Gynecol 171(4):1115-19, 1994.
23. Rosenn B, Miodovnik M, Combs CA, Khoury J, **Siddiqi TA.** Glycemic thresholds for spontaneous abortion and congenital malformations on insulin-dependent diabetes mellitus. Obstet Gynecol 84(4):515-20, 1994.
24. Rosenn BM, Miodovnik M, Holcberg G, Khoury JC, **Siddiqi TA.** Hypoglycemia: The price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. Obstet Gynecol 85(3):417-22, 1995.
25. **Siddiqi TA**, O'Brien Jr. WD, Meyer RA, Sullivan JM, Miodovnik M. *In situ* human obstetrical ultrasound exposimetry: Estimates of derating factors for each of three different tissue models. Ultrasound Med Biol 21(3),1995.
26. Bendon RW, Dungy-Poythress L, Miodovnik M, **Siddiqi TA.** Perinatal pathology of interhemispheric cyst with thinned posterior corpus callosum. Ped Path & Lab Med 16:299-317, 1995.
27. Miodovnik M, Rosenn BM, Khoury JC, Grigsby JL, **Siddiqi TA.** Does pregnancy increase the risk for development and progression of diabetic nephropathy? Am J Obstet Gynecol 174:1180-91, 1996.
28. Rosenn BM, Miodovnik M, Khoury JC, Siddiqi TA. Counterregulatory hormonal responses to hypoglycemia during pregnancy. Obstet Gynecol 87:568-74, 1996.
29. Rosenn BM, Miodovnik M, Khoury JC, **Siddiqi TA**. Deficient counterregulation: A possible risk factor for excessive fetal growth in IDDM pregnancies. Diabetes Care 20(5):872-74, 1997.
30. **Siddiqi TA.** Response to: Chauhan SP, Hendrix NW, Morrison JC, Magann EF, Devoe LD. Intrapartum oligohydramnios does not predict adverse peripartum outcome among high-risk patients. Am J Obstet Gynecol 176:1130-35, 1997.
31. Bragg BJ, Rosenn BM, Khoury JC, Miodovnik M, **Siddiqi TA.** The effect of early discharge after vaginal delivery on neonatal readmission rates. Obstet Gynecol 89(6):930-33, 1997.
32. Handwerger S, Datta G, Richardson B, Schmidt CM, **Siddiqi TA**, Turzai L, Anantharamaiah GM. Pre β HDL stimulates placental lactogen release from human trophoblast cells. Am J Physiol 276(2)(1):E384-89, 1999.
33. **Siddiqi TA**, Miodovnik M, Meyer RA, O'Brien Jr. WD. In vivo ultrasound exposimetry: Human tissue-specific attenuation coefficients in the gynecologic examination. Am J Obstet Gynecol 180(4):866-74, 1999.
34. Kovilam OP, Cahill W, **Siddiqi TA.** Pregnancy with mitochoindrial encepalopathy, lactic acidosis, and stroke-like episodes syndrome. Obstet Gynecol 93(5)(2):853, 1999.

OTHER SUPPORT

DONOVAN, EDWARD F., M.D.

520-N Ohio Department of Health
Child & Family Health Services, Women's and Children's Health Outcomes Program
Edward F. Donovan, M.D. - Principal Investigator
Effort: %
Current Grant Period: 07/01/00 - 06/30/01
Total Direct Costs: $ 152,206

Longitudinal cohort health outcomes analysis of children born to women with suboptimal prenatal care.

Private Support

Uma Kotagal, M.D. - Principal Investigator
Edward Donovan, M.D. - Co-Principal Investigator
Effort: %
Entire Project Dates & Costs: 01/01/99 - 12/31/02 $3,470,704
Current Grant Period & Costs: 01/01/99 - 12/31/01 $1,047,150

1. Development and implementation of the OKI Regional Center for Child Health Statistics
2. Development and implementation of School Health Demonstration Project

31-3-01-F-BM-320, Ohio Department of Health
Regional Perinatal Outreach Education Program
Edward F. Donovan, M.D. - Project Director
Effort: %
Current Grant Period: 10/01/99 - 09/30/00
Total Direct Costs: $ 96,016

1. Coordination of provider education in the Cincinnati birth cohort catchment area.
2. Maintenance of a population-based, birth and outcome, cohort database.

HD 27853-06, National Institutes of Health
Multicenter Network of Neonatal Intensive Care Units
Edward F. Donovan, M.D. – Principal Investigator
Effort: %
Current Grant Period: 04/01/96-03/31/01
Total and Indirect Costs $ 1,377,697

Collaborative clinical research focusing on randomized trials designed to improve newborn care and outcomes.

No overlap.

% = Percentage of Effort

OTHER SUPPORT

WARNER, BARBARA, MD

NONE

OTHER SUPPORT

STEICHEN, JEAN J., MD

NONE

OTHER SUPPORT

HABERMAN, BETH, MD

NONE

OTHER SUPPORT

SIBAI, BAHA M., MD

NONE

OTHER SUPPORT

FRIDRIKSSON, JON, MD

NONE

OTHER SUPPORT

JOBE, ALAN H., MD, PHD

NIH/NHLBI 1 P01 HL 61646-01A1
PPG/Surfactant Homeostasis in Health Disease
Project 1 - Alveolar Homeostasis of Surfactant Lipids and Proteins
Alan Jobe, MD, PhD - PI
Effort: %
Period: 08/10/99-06/30/04
Amount: $12,940
This is the same project that is funded primarily by NICHD by agreement with NHLBI as R01-HL 11932-21 - Lung Phospholipid Appearance and Stability

NIH/NHLBI 1 P01 HL 61646-10A1
PPG/Surfactant Hoemeostasis in Health Disease
Administrative Core - Alan Jobe, MD, PhD - PI
Effort: %
Period: 08/10/99-06/30/04
Amount: $7,500
This PPG will explore the mechanisms responsible for surfactant homeostasis using transgenic mouse models. This project will characterize the alveolar forms ofsurfactant and the associations of the surfactant proteins with the lipids. A goal is to learn which alveolar cell types participate in surfactant component clearance and catabolism.

NIH/NICHHD R01 HD 12714 21
Developmental Lung Phospholipid Metabolism
Alan Jobe, MD, PhD - PI
Effort: %
Period: 07/02/97-02/29/00
Amount: $147, 857
This project is to study surfactant metabolism and lung injury in a preterm lamb model of respiratory distress syndrome. Studies include evaluations of indicators of injury and surfactant function in the preterm.

NIH/NHLBI 5 R01 HL 56285 03
Structure/Function Analyses of SP-B in Transgenic Mice
Timothy Weaver, PhD - PI
Effort: %
Period: 05/01/96-04/30/01
Amount: $219,177
This is a project to characterize surfactant metabolism in transgenic mice with SP-B deficiency and subsquently with altered SP-B genes.

% = Percentage of Effort

NIH/NHLBI R01 HL 63329-01
Role of Surfactant Protein D In Surfactant Homeostasis
Machiko Ikegami, MD, PhD - PI
Effort: %
Period: 06/01/99-05/31/04
Amount: $228,000
This project is to study the SP-D knock out mouse to learn how SP-D modulates surfactant homeostasis and host defenses.

% = Percentage of Effort

OTHER SUPPORT

HEUBI, JAMES E.

ACTIVE

MO1 RR08084 (PI:Boat/PD:Heubi) 12/01/96-11/30/01 %
NIH/NCRR 1,305,231
General Clinical Research Center

Inpatient unit at Children's Hospital with outpatient, scatter bed, and Core Laboratory facilities. Major areas of research: pediatric liver disease, cholera challenge study, diabetes mellitus, cystic fibrosis-gene therapy, bone disease, growth hormone, Gaucher disease, cancer prevention and treatment, and transplantation immunology.

FDR 001277 (Heubi) 4/1/99-3/31/01 %
FDA $122,664
Tauroursodeoxycholic Acid Prophylaxis for TPN Cholestasis

This project will evaluate the effect of an orphan drug, ursodeoxycholic acid, on the development of liver and biliary tract disease in neonates.

T32 DK07727 (Cohen) 01/01/95-11/30/99 (no cost extension) %
NIH/NIDDK $135,704 (no salary support)
Pediatric Gastroenterology and Nutrition Training Grant

The goals of this grant are to provide the intensive basic and clinical research experience that is essential to prepare M.D.'s and Ph.D.'s for productive and independent careers in academic medicine.

P01 DK 54504 (Hui; Heubi Core PI) 03/01/99-02/29/04 %
NIH/NIDDK $132,140 (subcontract)
Molecular Mechanisms of Cholesterol Absorption

The goal of this project is to study the relationship between bile acid composition, dietary fatty acids, and plasma lipids and cholesterol absorption, synthesis and LDL-receptors.

R01 CA 73328 (Setchell) 9/30/96-8/30/99 (no cost extension) %
National Cancer Institute $196,371
Metabolic Fate and Plasma Kinetics of Dietary Soy Isoflavones

The goal of this project is to improve our understanding of the factors that determine the plasma levels, bioavailability, and kinetics of isoflavones in women and men, how these are influenced by the type and amount of soy food matrix, and chemical composition, whether there are gender or age-related differences in metabolism and bioavailability and if intestinal transit influences metabolism.

FD-R-001439-01 (Setchell) 09/30/97-09/29/00 %
FDA RFA $98,500
TUDCA for the Treatment of Hepatobiliary Disease in CF

The purpose of this project is to evaluate the potential advantages of therapeutic doses of TUDCA (tauroursodeoxycholic acid) over UDCA (ursodeoxycholic acid) for treatment of cystic fibrosis patients with liver disease.

% = Percentage of Effort

OTHER SUPPORT

James E. Heubi, M.D. (Continued)

ACTIVE, continued

FD-R 001537 (Wenstrup) 1/1/98-12/31/01 %
FDA $198,006
Anti-Resorptive Bone Therapy for Osteopenia in Gaucher Disease

The purpose of this project is to determine whether the osteopenia that is seen in most adults with Gaucher Disease can be corrected by anti-resorptive adjunctive therapy in patients with Gaucher Disease who are receiving enzyme therapy.

PENDING

Pending Support

OVERLAP

There is no scientific, budgetary or effort overlap in any of the grants listed for James E. Heubi.

SIDDIQI, TA

ACTIVE

HD-27905-06 (Miodovnik) 01/01/96 - 03/31/01 %
NIH $227,915
Multicenter Network of Maternal-Fetal Medicine Units

The Maternal-Fetal Medicine Unit (MFMU) is a network of 11 centers established by NICHD to conduct longitudinal, multicenter, clinical trials concentrating on obstetrics, especially the prevention of low birth weight. The goal of the network is to enable investigators to conduct studies using a much larger, more diverse patient population than would otherwise be available. The network allows researchers to develop new ideas for protocols for clinical trials, conduct trials faster and more efficiently, and carry out more studies with more subjects.

HD 21687-09 (Siddiqi) 04/01/95 - 08/31/00 %
NIH $631,290
Human Ultrasound Dosimetry in Ovarian, Embryonic and Fetal Examinations

(1) To determine the maximum values of ultrasonic quantities to which the human embryo and fetus are exposed during a pulsed Doppler (including colorflow Doppler) ultrasound examination. (2) Use our experimentally obtained *in-situ* data to evaluate the validity and accuracy of the Overlying Tissue Model versus the Fixed Attenuation Model. (3) Develop a quantitative five layer tissue model in humans to determine the coefficient of attenuation when an ultrasound beam passes through each of the following maternal tissues: (i) skin, (ii) subcutaneous fat, (iii) skeletal muscle, (iv) fascia, and (v) myometrium.

PREVIOUS GRANTS

HD-21687-06A1 (Siddiqi) 01/01/91 - 03/31/95 %
NIH $853,493
Human Ultrasound Dosimetry in Ovarian, Embryonic and Fetal Examinations

(1) To determine the maximum values of ultrasonic quantities to which the human embryo and fetus are exposed during a pulsed Doppler (including colorflow Doppler) ultrasound examination. (2) Use our experimentally obtained *in-situ* data to evaluate the validity and accuracy of the Overlying Tissue Model versus the Fixed Attenuation Model. (3) Develop a quantitative five layer tissue model in humans to determine the coefficient of attenuation when an ultrasound beam passes through each of the following maternal tissues: (i) skin, (ii) subcutaneous fat, (iii) skeletal muscle, (iv) fascia, and (v) myometrium.

HD-21687-01A1 09/01/87 - 08/31/90 %
NIH $271,979
Human Ultrasound Dosimetry in Ovarian, Embryonic and Fetal Examinations

(1) To determine the maximum values of ultrasonic quantities to which the human embryo and fetus are exposed during a pulsed Doppler (including colorflow Doppler) ultrasound examination. (2) Use our experimentally obtained *in-situ* data to evaluate the validity and accuracy of the Overlying Tissue Model versus the Fixed Attenuation Model. (3) Develop a quantitative five layer tissue model in humans to determine the coefficient of attenuation when an ultrasound beam passes through each of the following maternal tissues: (i) skin, (ii) subcutaneous fat, (iii) skeletal muscle, (iv) fascia, and (v) myometrium.

% = Percentage of Effort

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinen capabilities, relative proximity, and extent of availability to the project. Use "Other," identify support services such as machine shop, electronics shop, and specif the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:	Extensive contiguous laboratories for Pulmonary Biology Faculty Core labs for: Physiology, Anatomy and Morphometrics, Confocal Microscopy, Transgenics Facility, Full Services, microanalyzer clinical laboratories at each participating NICU
Clinical:	Three level 3 units serving 30,000 regional deliveries
Animal:	Complete vivarium facilities for mice, other small animals and sheep. AAALAC approved.
Computer:	Networked computers for all faculty and a computer equipped office for all neonatal fellows.
Office:	Separate office space for all neonatal fellows and staff. Many fellows have a desk in the research laboratory in which they are working.
Other:	Access to research facilities of other research groups at the Children's Hospital Research Foundation (CHRF including the Department of Molecular and Developmental Biology.

MAJOR EQUIPMENT:

See following description of available resources, pages 36 to 49.

1. The University of Cincinnati College of Medicine and the University Hospital (UH)

The Medical College of Ohio was founded in 1819 in Cincinnati through the efforts of Daniel Drake. In 1821, Drake established the Cincinnati Community Hospital and Lunatic Asylum for care of medically indigent and as a source of teaching patients. He developed teaching methods which provide the basis for medical education today. In 1896, the Medical College of Ohio became part of the University of Cincinnati while the Community Hospital was administered by the City of Cincinnati. In 1914, Cincinnati General Hospital was built and subsequently geographic full time departmental directors were recruited in the Departments of Medicine, Pediatrics and Surgery. In 1961, the University appointed a Vice-President in charge of medical affairs and in 1962, the University of Cincinnati assumed responsibility for the Cincinnati General Hospital.

In 1969, a new 600 bed University Hospital replaced the Cincinnati General Hospital. The Medical Sciences Building, which is physically joined to the Hospital, contains all the preclinical and clinical departments of the College of Medicine (except Pediatrics), the health science library, classrooms, teaching laboratories, 200 research laboratories totaling 210,235 sq ft, and animal facilities. Full time faculties were established during the 1960-70's in Psychiatry, Obstetrics and Gynecology, Dermatology, Anesthesiology, Ophthalmology, Otolaryngology, Neurosurgery, Orthopedics, Neurology and Physical Medicine. There was also considerable growth in the departments of Pharmacology, Pathology, Biochemistry and Anatomy. In 1977, the University of Cincinnati with its College of Medicine became members of the State of Ohio University System and the Cincinnati General Hospital was renamed the University Hospital. The College of Medicine is housed in the Medical Sciences Building which is directly across Bethesda Avenue from the current GCRC. Biomedical research grants and contracts, stimulated by the construction of the Medical Sciences Building in 1974, the Cardiovascular Building in 1996 and most recently the Vontz Center for molecular Studies in 1999, have steadily increased. There has been a significant growth in total grant funding to the University of Cincinnati over the last 5 years. The UC Medical Center was awarded $73 million in research grants from both government and non-government sources in FY 1999.

During the 1980's and 90's, the faculty expanded particularly in the Departments of Medicine, Pediatrics, Surgery, Physiology, and Molecular Biology, Biochemistry and Microbiology. Full time faculty at the University of Cincinnati has now reached 915 distributed among 4 basic science and 18 clinical departments with 254 in Pediatrics, 128 in Internal Medicine, 85 in Surgery and its subspecialties, 38 in Family Medicine, 27 in Obstetrics and Gynecology, 56 in Radiology, 44 in Psychiatry, and 22 in Anesthesia.

Over the past year the University of Cincinnati College of Medicine (UC-COM) and the UC Medical Center (UCMC), including Children's Hospital and Research Foundation, have developed a 5-year plan as part of a broader, comprehensive UCMC Plan for the Millenium. In addition to improving medical and graduate student education and patient care, the plan places a major emphasis on basic and clinical research. The overall goal is to double funding for extramurally sponsored research over the next five years. To capitalize on data emerging from the Human Genome Project, UCMC has recently begun a major initiative in Expression Technology, establishing core facilities in functional genomics, proteomics and bioinformatics. This effort is underpinned by a recent award from the Howard Hughes Medical Institute as part of the Biomedical Research Support Program for Medical Schools. Other major initiatives include establishing a new research institute, significant recruitment of new faculty, expansion of capabilities in neuroimaging and x-ray crystallography, obtaining funding for a satellite GCRC (for study of adults unsuitable for the GCRC at the Children's Hospital) and Cancer Center, and continued support for core infrastructure in DNA sequencing, biostatistics-experimental design, clinical trials, structural biology, transgenic and gene-altered mice, mouse phenotyping and lab animal medicine. Clinical research will assume more of a disease-focus. Interdisciplinary groups will study specific diseases in several areas (cancer, developmental disorders, cardio-pulmonary and neurodegenerative diseases, environmental influences, ischemic and infectious diseases), integrating basic science with translational research, patient-oriented research and clinical trials. Another important goal is to continue our efforts in research training of about 600 research trainees (physician-scientists, graduate students and postdoctoral fellows). UCMC has made great progress in research in the past three years, having increased sponsored program funding by 30% to about $120M and anticipates continued growth into the new millenium.

2. The Children's Hospital Medical Center (CHMC)

The Children's Hospital was founded in 1883 as the Hospital of the Protestant Episcopal Church in the Diocese of Southern Ohio. Thirty-eight patients were treated in the first 7 months in the 12 beds of a three-bedroom, one bathroom house. In 1887, the hospital moved to a 20-bed facility in Mount Auburn and by

1889, the staff of 10 included surgeons, general physicians, oculists, dentists, and a neurologist.

The Children's Hospital was relocated to its present site across the street from the College of Medicine in 1926. Subsequently, William Cooper Procter, a benefactor of the hospital, provided a building to be devoted to research in children's diseases and a $2.5 million endowment. This institution, designated the Children's Hospital Research Foundation, was dedicated in 1931. One of the first workers in the Research Foundation was Josef Warkany, a physician destined to become world renowned for his investigations in teratology. During World War II, investigators from Children's Hospital and Paul Hoxworth at the University of Cincinnati developed methods to preserve whole blood that allowed it to be air-transported world-wide and stored long enough to be of use in field hospitals. Additional notable contributions from the Children's Hospital Research Foundation have included seminal work which led to means of effective cardiopulmonary bypass used during repair of congenital heart defects and the outstanding contributions of Albert Sabin which led to the development of an oral "live" polio vaccine with virtual eradication of polio as a major health hazard. Children's Hospital investigators have also included Leland Clark, inventor of the oxygen electrode, and more recently Dr. Jeffrey Whitsett, whose seminal work with pulmonary surfactant apoproteins were key to the development of strategies to treat respiratory distress syndrome of the newborn.

Today, Children's Hospital is still one of only 5 children's hospitals with a major endowed research foundation. The Children's Hospital and its Foundation are among the top 3 pediatric centers in the country in areas of patient care, education and research. The Children's Hospital Medical Center is a 306-bed private hospital that serves as the major teaching facility for pediatrics. It is the largest pediatric hospital in the United States with the largest number of inpatient beds, annual visits to the emergency facilities, and outpatient and total surgical procedures. It is the only hospital in the Cincinnati metropolitan area, with a population of 1.7 million people, which hospitalizes "sick" children. Subspecialists serve the needs of children in the surrounding region and nationally. Children's Hospital has multiple unique programs including bone marrow and stem cell transplantation, solid organ transplantation (liver, kidney, heart), and a Level 1 Trauma Center. Since 1980, research grant support for investigators at Children's Hospital has increased from $4.4 million to greater than $42 million for FY 1999. The Children's Hospital Medical Center now has 530,000 gross square feet of research space. There is a 59,000 square foot vivarium, including a large area for surgical research. Construction is currently underway (completion date: Fall 2000) for 110,000 additional square feet of laboratory space to provide offices for support personnel such as in areas such as biostatistics, epidemiology, or outcomes research and additional wet laboratories.

3. Department of Pediatrics

The Department of Pediatrics of the University of Cincinnati College of Medicine is largely housed within the Research Foundation of Children's Hospital Medical Center, with a small component of a variety of activities including health care delivery and pharmacology located in the Medical Sciences Building of the College of Medicine. All faculty at the Children's Hospital have academic appointments in the College of Medicine. There has been substantial growth in the faculty in the Department of Pediatrics in the past five years. At present there are 26 divisions within the department and over 240 full-time faculty. These faculty are primarily in three different academic tracks; 97 are in the clinical track, 54 in the research track and 81 tenured or in the tenure track, and 10 in field service. In FY 1999, there were 34 new faculty appointments. The size of the faculty has increased 70% over the past 6 years and will continue to expand. These numbers reflect growth that is driven by needs and opportunities in all areas of the medical center. In addition, there are about 75 volunteer faculty appointments that include community pediatricians involved in various teaching programs of the department.

The Children's Hospital Research Foundation (CHRF) provides research administration for the Children's Hospital Medical Center. Dr. Thomas F. Boat is director of the Research Foundation and Chair of the Department of Pediatrics and Principal Investigator of the GCRC. The Department of Pediatrics is currently training 103 clinical fellows, covering nearly all of the sub-specialty areas, and 57 research or post-doctoral fellows. In addition, up to 6 Procter Scholars are supported annually. These individuals are identified as having particular promise as investigators and are starting on a two or three year course of intensive research experience as a second or third year fellow or as a transitional faculty member. The department also trains 125 residents, including 84 in categorical pediatrics and 41 in combined Medicine/Pediatrics. In the current first year resident class, we have recruited 5 individuals with combined M.D. and Ph.D. degrees. This reflects a strategy of recruiting individuals who are committed to a career of medicine and science at an early stage in

their development and tracking these people into research-intensive training programs. Eight residents recently presented papers at our annual Edward L. Pratt Pediatric Residency Research Symposium.

During this past year, CHMC has emerged as the third largest child health research effort in the country as measured by NIH funding. Research programs of the department and foundation are growing rapidly, as evidenced by an NIH award budget increase from $6.5 million in fiscal year 1993 to nearly $21 million (annual direct costs) in fiscal year 1999 (see charts on next page). Total sponsored program awards (direct and indirect) to the Children's Hospital Research Foundation in 1999 exceeded $42 million and an additional $1 million was awarded to Pediatric investigators through the UC College of Medicine Sponsored Program Office. A significant amount of funding is obtained from the Cystic Fibrosis Foundation, the American Heart Association, the March of Dimes and the Arthritis Foundation. The FY 1998 success rate for new and renewal of NIH proposals was 47% and 75% respectively, well above NIH averages. While the success rates in FY1999 were a bit lower (25% for new NIH grants and 63% for competitive renewals) they still are above the national average. The Department of Pediatrics holds 6 NIH-funded Institutional T32 Post-doctoral and pre-doctoral training grants that support 40 postdoctoral fellows and 38 predoctoral students (see below). In addition, eight mentored grants (K08s) have been awarded to junior faculty from the NIH. The research activity of the Children's Hospital Research foundation is also reflected in their publication activity. Investigators within the department published over 500 research papers in peer-reviewed (326) and non-peer reviewed literature in fiscal year 1999.

The Research Foundation and the Department of Pediatrics are committed to the early development of scientific careers of its faculty members. The large number of senior investigators in the Foundation provide an opportunity for the most effective mentorship of young investigators. The department is actively involved in tracking the progress of young investigators, of nurturing their scientific activities, and actively protecting their time to achieve their research goals.

The CHRF and the Department of Pediatrics are committed to research that impacts practice and improves child health. **Clinical Science has received the greatest attention in the last 5 years. Fully 1/3 of all research funding to the CHRF from external sources supports clinical research. It is the goal of the Foundation that this proportion will reach 50% by the year 2003. The Board of Trustees of the CHMC has provided funds to recruit faculty with outstanding skills in biostatistics, epidemiology, health services research, and new modalities of body imaging to provide core expertise for the clinical sciences.** The Mission of the CHRF includes "the translation of new knowledge into novel diagnostic and therapeutic approaches to the care of children thus ensuring that patients at Children's Hospital will receive the most advanced care available and positioning Children's to attract patients from extended geographic areas." The overall philosophy of research at CHRF is to pursue research areas that will lead to application to clinical settings. "Whenever possible, investigators will be expected to consider the importance of the research questions that they address for the medical, surgical and behavioral care of children of all ages, and will be encouraged to assume a leadership role or actively collaborate in bringing the results of their studies to clinical application. This expectation will be supported by the provision of core clinical research facilities as well as opportunities to train in the clinical sciences or work with clinical scientists of the first rank.".

4. The Department of Pediatrics of the University of Cincinnati College of Medicine:

The Research Foundation and Children's Hospital Medical Center share a close relationship and are integrated under the same Board of Trustees. Research and teaching, the two major objectives of Children's Hospital, is documented in the following quotation from Article I, entitled Design, Purpose, and Intent of the bylaws of the Board of Trustees of the Hospital: "The board of trustees affirms its belief that the immediate bedside car of the sick reaches its highest effectiveness in a hospital which fosters the pursuits of learning, and that . . . patient care, teaching, and research are complementary and supplementary to each other."

A written agreement establishes the position of Children's Hospital and Children's Hospital Research Foundation as major teaching facilities for the University of Cincinnati College of Medicine. Moreover, the Chairman of the Department of Pediatrics within the College of Medicine also serves as the Director of Children's Hospital Research Foundation. He is chosen by a committee of the College of Medicine and his/her appointment must be approved by the Boards of Trustees of both the University of Cincinnati and Children's Hospital.

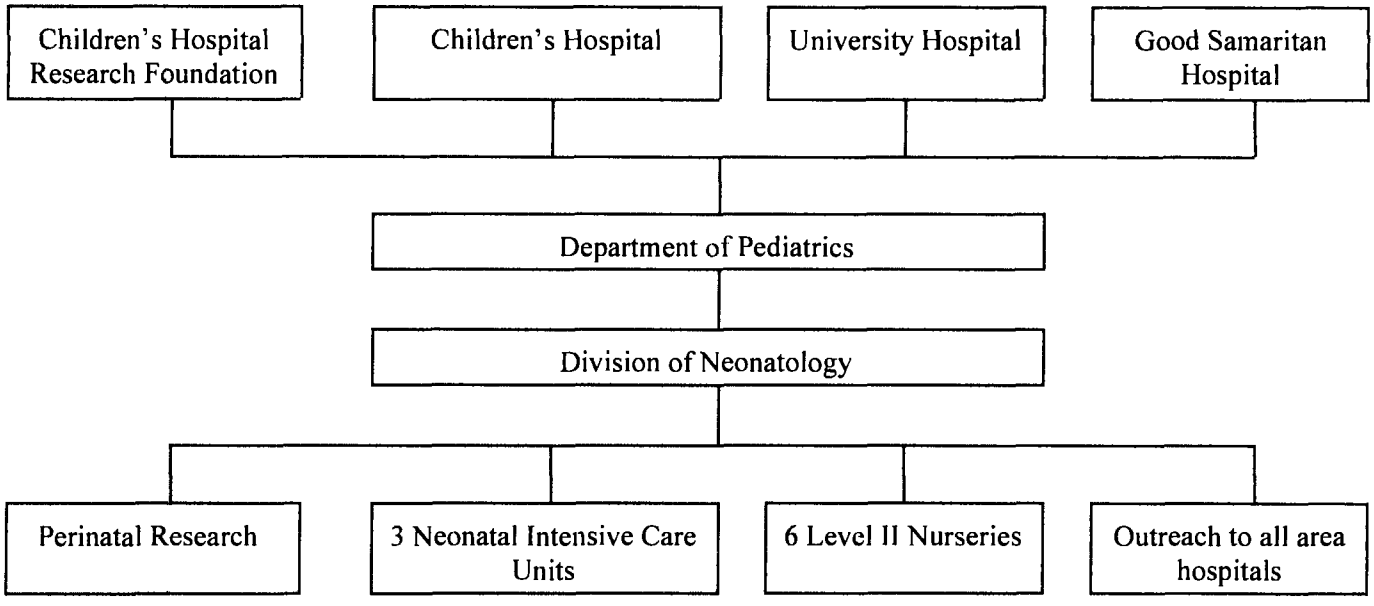
The Children's Hospital is a private hospital and the University is a state university; however, all pediatric faculty hold appointments at the College of Medicine. Faculty appointments to the Children's

Hospital have to be approved by the Dean of the College of Medicine. Thus, the academic line of command runs from the Dean through the chairman to the faculty, even though pediatric faculty based at Children's Hospital are usually directly salaried by Children's Hospital. NIH grants based predominantly at the College of Medicine are routed through the College of Medicine. Faculty who are based at Children's Hospital or at Children's Hospital Research Foundation are administratively subcontracted for the grant, since Children's Hospital Medical Center is technically a "private" institution. Several members of the pediatric faculty, such as Dr. Tsang, are directly salaried by the University and based predominantly at the University College of Medicine. As such, these faculty do not need to be subcontracted.

Additional factors have supported the cohesive interrelationship between the two institutions: 1) from the first, all members of Children's Hospital Research Foundation have held joint appointments on the faculty of the College of Medicine; and 2) at least 25 faculty members of the Department of Pediatrics hold joint appointments in other departments of the College of Medicine. At present, there are at least 20 Divisions within the Department of Pediatrics and 150 full-time staff members with academic appointment. This staff has maintained a high standard for productive research into diseases of childhood.

Shortly after the founding of Children's Hospital Research Foundation, a Scientific Advisory Committee, composed of eminent scientists external to the institution, was formed primarily for the purpose of evaluating the caliber of research done in the institution. The committee meets annually and has been extremely successful in carrying out its responsibilities to the Director and Research Committee of the Board of Trustees.

In addition to research activity and teaching responsibilities, the Division of Neonatology has direct responsibility for newborn services at Children's Hospital (Regional Center For Newborn Intensive Care), University Hospital (Neonatal Intensive Care Unit and Term Nurseries), and Good Samaritan Hospital (Neonatal Intensive Care Unit and Term Nurseries) and 6 level II hospitals in the region. The Division of Neonatology has outreach education responsibilities for all 19 area obstetrical hospitals in a 30,000 delivery, 30 mile radius catchment area for primary, secondary and tertiary perinatal care. A secondary catchment area extends to approximately 60 mile radius for "quartenary" referrals such as ECMO; and undertakes special infant follow-up programs. The integration of neonatal services throughout the city under one Division of Neonatology is unique in this country and adds to the strength of research capabilities within the Division of Neonatology. The relationships between the Division of Neonatology and other departmental components are illustrated as follows:



5. The Health Alliance of Greater Cincinnati

In January 1995, the Board of Trustees of the University of Cincinnati agreed to align the University Hospital with four other hospital systems within the Greater Cincinnati area as a not-for-profit organization. The three other institutions include The Christ Hospital, the St. Luke's Hospitals (located in northern Kentucky) and the Ft Hamilton-Hughes Hospitals (located in the northeast region of Cincinnati). The organization and its

hospitals operate under a single set of strategic objectives carried out both collectively and individually although each retains its own corporate structure and Board of Directors. The operating plan calls for the development of a well-integrated health care delivery network that offers a full range of services and is focused on quality and cost effectiveness. The hospitals and physicians that make up The Health Alliance of Greater Cincinnati share a common mission: to improve the health of the people of Greater Cincinnati through an integrated health care delivery system serving the community with cost effective pricing and health services of the highest quality. As the principal teaching and research institution within The Alliance, the University Hospital will be strengthened in this mission by its association with the other institutions within The Alliance.

6. Patient Resources Available for Research

The Children's Hospital Medical Center (CHMC) is the largest pediatric facility in the United States based upon inpatient beds, annual admissions, total surgical procedures, outpatient surgical procedures and emergency department visits. It is the only hospital in the metropolitan area, with a population of 1.7 million people, which hospitalizes "sick" children. Its subspecialists not only serve the needs of children in the surrounding region but also, to some extent, nationally. The Children's Hospital has multiple unique programs including bone marrow transplantation, solid organ transplantation (liver, kidney, heart), and a Level I Trauma Center. There were 305 beds and in 1999, there were 10,747 medical admissions, and 3,155 surgical admissions. There were a total of 36,486 primary care and 250,077 subspecialty care outpatient visits, and 80,974 visits to the emergency department. In 1999, Children's Hospital surgeons performed 21,508 surgical procedures including 18 kidney transplants, 21 liver transplants, and 4 heart transplants. There were 49 stem cell transplants performed. There are 5 satellite outpatient facilities of the Children's Hospital located in the greater metropolitan area. Additional outpatient satellites are currently being planned, including a facility in Northern Kentucky.

University Hospital is the largest teaching hospital in the region with 695 beds and is the major referral center for many programs and therapeutic modalities not available elsewhere. Included in these unique programs are a Level-1 trauma center, the Barrett Center for Cancer Prevention, Treatment and Research, one of the nations largest level-three neonatal intensive care units and an outstanding Center for Reproductive Health. Recent initiatives have included development of centers of excellence in cardiovascular disease, neurosciences, and pulmonary medicine. In FY 1999, physicians at University Hospital had over 200,000 patient encounters: with 22,181 inpatients; 168,262 outpatients; and 73,147 emergency department visits. There were 2,271 births at University Hospital. A total of 11,077 surgical procedures were performed at the University Hospital including 65 kidney and kidney/pancreas transplants and 57 heart and liver transplants.

Good Samaritan hospital provides perinatal services for approximately 4800 deliveries a year. Four, board-certified perinatologists provide consultation and/or management (outpatient and inpatient) of high-risk obstetrical patients. The Seton Center located one floor below labor and delivery offers high level ultrasonography and minimally invasive testing. More invasive interventions such as cordocentesis are done within labor and delivery. There is a 21 bed high risk antepartum unit which typically runs at or near capacity and is in the process of renovation and expansion. There are 4 additional high risk beds located within labor and delivery. Admissions to the inpatient high risk service include maternal transports from other community hospitals which number approximately 180 per year. There are 12 labor and delivery suites and 41 single postpartum rooms, which can be converted to double occupancy as required.

There is a newly renovated 46 bed NICU located next to labor and delivery with 650-700 annual admissions. Since opening April 2000, average daily census has been 40. The NICU is staffed by 7 University of Cincinnati neonatologists, 42 full and 42 part-time NICU nurses, 9 full and 7 part-time respiratory therapists and 1 part-time nutritionist. On-site support in subspecialty areas such as ophthalmology, pediatric cardiology (including echocardiography) and pediatric surgery is provided through the Children's Hospital Medical Center.

7. Institutional Assets for Research and Research Training

Children's Hospital Medical Center and the University of Cincinnati Medical Center are the region's major centers for medical education. More than 80 percent of the pediatricians and pediatric nurses and a significant number of allied health professionals currently practicing in the region received their training at Children's Hospital. The University of Cincinnati is the source of medical training for over 70 percent of the pharmacists, over 60 percent of the nurses and over 50 percent of the physicians in the area.

There are 622 medical students and 357 graduate students enrolled at the University of Cincinnati College of Medicine. The M.D./Ph.D. program, which was initiated in 1985, now has 31 students. Enrollment in the

College of Pharmacy includes *213* undergraduates and *96* graduate students. There are 497 undergraduate and 121 graduate students in the School of Nursing. Forty-five of the graduate students are in the five-year old Ph.D. program. During Fiscal 1999, there are 481 house officers at the University Hospital and 84 pediatric house officers, 27 medicine/ pediatric residents, 6 Psychiatry/Child Psychiatry/Pediatric residents, 3 Human Genetics/Pediatric residents, 5 pediatric physical medicine and rehabilitation residents, 3 psychology residents, and 10 dental residents at the Children's Hospital for a total of 615 residents training in 24 programs. At the University of Cincinnati Medical Center, there are 67 clinical (M.D.) postdoctoral fellows in training in 10 departments or divisions and an additional 36 research (M.D. or Ph.D.) fellows being trained in clinical or basic science departments. At CHMC there are 103 M.D.or M.D./Ph.D. clinical and research postdoctoral fellows and 57 Ph.D. postdoctoral fellows in training.

The University of Cincinnati College of Medicine has a subsidy from the State of Ohio for Clinical Teaching and Research. At the Children's Hospital, the training of postdoctoral fellows is funded largely by institutional funds of the Children's Hospital Research Foundation. Currently there are 6 training grants for postdoctoral fellows (M.D. or M.D./Ph.D.) with funding from the NIH, which can provide fellows for use of the GCRC facility as portions of their research projects:

Pediatric Rheumatology Training
Developmental and Perinatal Endocrinology Training
Pediatric Gastroenterology and Nutrition Training
Cardiovascular and Molecular Biology in the Young
Research Training in Pediatric Nephrology
Pulmonary and Cardiovascular Development Training

In 1990, the Children's Hospital Research Foundation offered, for the first time, a Clinical Research Fellowship. The goal of this program is to train talented young pediatricians for academic careers in clinical research. The program has had 16 fellows, 11of whom have completed the program. Six of the 11 completing the programs have gone on to academic positions in which part of their activity includes clinical research including 3 who are currently on the faculty of the Department of Pediatrics in Cincinnati. The fellowship program is directed by Steven Daniels, M.D., Division of Cardiology, and C. Ralph Buncher, Ph.D, Department of Environmental Health. The program is individualized depending upon the interests and level of experience of the trainee. Faculty members from the Divisions of Gastroenterology and Nutrition, Cardiology, Endocrinology, Hematology/Oncology, Neonatology, Infectious Disease (Pediatrics) and Epidemiology/Biostatistics (Environmental Health) serve as mentors for trainees. During the first year, the trainee takes courses in the Epidemiology curriculum including Introduction to Biostatistics, Introduction to Epidemiology, Use of the Computer in Medical Science, Regression Analysis, Experimental Design, Use of Statistical Procedures in Computer Package Programs, and Special Topics in Epidemiology. These courses allow the fellows to participate in the design and analysis of ongoing clinical research studies. During the second year, course work may include Survival Analysis and Applied Multivariate Analysis. Additional courses will be available but not required including Statistics in the Pharmaceutical Industry, Genetic Epidemiology, Epidemiology of Cancer, Nutritional Epidemiology, Classic Topics in Epidemiology, Reproductive Epidemiology, Rates and Proportions, Statistical Methods in Epidemiology, Nonparametric Statistics, and Cardiovascular Epidemiology. Initially, fellows work with a faculty mentor on an ongoing protocol. With completion of the basic curriculum, they develo and begin execution of a protocol of their own design. This program leads to a Master of Science degree and is designed to produce young faculty members who are especially suited to executing successful clinical research projects.

Children's Hospital Research Foundation/University of Cincinnati

The total grant funding to the University of Cincinnati Medical Center including the College of Pharmacy and College of Nursing for Fiscal Year 1999 was $73,024,163. This includes $56,297,672 from the National Institutes of Health, $4,137,656 from foundations including $940,480 from the American Heart Association, $7,465,498 from other federal agencies including NIOSH/CDC, EPA, and the Department of Defense, $3,186,149 from industry and $1,005,876 from the State of Ohio.

Total grant funding to the Children's Hospital Research Foundation for fiscal 1999 is $42,062,227 of which $28,522,637 is from the National Institutes of Health. Total federal funding is $31,343,280 and an additional $4,128,526 from foundations such as Cystic Fibrosis Foundation, American Heart Association, Arthritis Foundation, and the Health Foundation of Greater Cincinnati. Over the last 7 years, NIH funding to the

Children's Hospital Research Foundation (CHRF) has more than tripled. Shown below is total funding to the CHRF for the last 7 years:

The combined total funding to the University of Cincinnati and the Children's Hospital for FY 1999 is $106,998,564.

Center Grants and Program Project Grants (including P30, P01, P50, P60, and U01 awards) at University of Cincinnati and Children's Hospital Medical Center include:

(1.) General Clinical Research Center (RR08084-07)
P.I. Thomas F. Boat, M.D., PD: James E. Heubi, M.D.
Project Period: 12/01/93-11/30/01
Current year Total Costs: $1,612,827

(2.) Multipurpose Arthritis and Musculoskeletal Diseases Center (AR 44059-03)
P.I.: David Glass, M.D.
Project Period: 7/01/96-5/31/01
Current Year Total Costs: $836,037

(3.) Cincinnati Comprehensive Sickle Cell Center (HL 58421-02)
P.I.: Clinton Joiner, M.D.
Project Period: 4/10/98-3/31/03
Current Year Total Costs: $1,537,586

(4.) Pediatric Pharmacology Research Unit (HD 37249-01)
P.I. R. Floyd Sallee, M.D., Ph.D.
Project Period: 1/07/99-12/31/03
Current year Total Costs: $264,528

(5.) Therapeutics Development Network (NCRR/Cystic Fibrosis Foundation)
P.I.: Robert Wilmott, M.D.
Project Period: 7/01/98-6/30/03
Current Year Total Costs: $162,000

(6.) Cooperative Multicenter Network of NICUs (HD 27853-05)
P.I.: Edward Donovan, M.D.
Project Period: 4/1/96-3/31/01
Current Year Total Costs: $180,261

(7.) Molecular mechanisms of cholesterol Absorption
P.I.: David Hui, Ph.D.
Project period: 3/01/99-2/29/04
Current year Total Costs: $1,073,725

(8.) Clinical Trial and Observation Study of the Women's Health Initiative (WH42126-02)
P.I.: James Liu, M.D. (UC)
Project Period: 9/30/94-6/30/05
Current Year Total Costs: $945,247

(9.) NIDA/VA Substance Abuse Medication Development Center (Y01-DA50038-05)
P.I.: Eugene C. Somoza, M.D., Ph.D.
Project Period: 10/1/95-9/30/00
Current Year Total Costs: $755,330

(10.) Center on Environmental Genetics (ES06096-08)
P.I. Marchall W. Anderson, Ph.D.
Project Period: 9/30/97-3/31/02
Current Year Total Costs: $323,306

(11.) SCOR in Heart Failure (HL52318-05)
P.I.Gerald Dorn, M.D.
Project Period: 1/01/00-12/31/04
Current Year Total Costs: $1,780,700

8. Relationships between the Division of Neonatology and the Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Division.

The Division of Neonatology, Department of Pediatrics, and the Department of Obstetrics and

Gynecology have been integrated closely for at least 30 years. Interrelationships between the Obstetrical Division and the Division of Neonatology include joint appointments in the Department of Pediatrics for most members of the Obstetrical Division, joint appointments in Obstetrics and Gynecology for most members of the Division of Neonatology, joint planning of improved perinatal care, joint fellowship training and postgraduate courses, and joint patient responsibilities and research endeavors.

9. Biostatistical and Data Management Support

The Child Health Statistics Center was founded January, 1999 with a $1.5 million 4-year grant from The Health Foundation of Greater Cincinnati. Dr. Edward Donovan (current Cincinnati PI for the NICHD Neonatal Research Network) is Principal Investigator and Director of the Child Health Statistics Center (CHSC). The Center is a collaboration between technical support staff and statisticians at the University of Cincinnati's Institute for Health Policy and Health Services Research and investigators in the Department of Pediatrics at Children's Hospital Medical Center. Technical staff include database developers/managers, analysts and data audit/edit/entry personnel.

The mission of CHSC is to provide useful information to tristate child health decision makers and policy makers by the support and dissemination of high-quality, population-based analysis and research. Current projects include: (1) an annual population-based report on the well-being of children in the Greater Cincinnati area, (2) a population-based, risk-adjusted analysis of the impact of site of delivery on very low birth weight mortality and morbidity (presented at Society for Pediatric Research, Boston, May 2000), (3) initiation of a representative, regional longitudinal, birth cohort study of the antecedents of childhood and adult disease and (4) technical assistance for a number of pediatric investigators using large data sets in their research.

Dr. Donovan' s direction of both CHSC and the Network grants provides great opportunity for support of Network-approved secondary and ancillary studies using datasets generated by the Network.

Judy Bean, Ph.D. was recruited as the biostatistician for the GCRC after an extensive nationwide search in 1998. She replace Shumei Guo, Ph.D. who had served as the biostatistician for the GCRC; however, she was not on site and her interaction with potential investigators as well as investigators of the GCRC was not ideal because of geographic problems. This weakness of the last review has been corrected with the recruitment of Dr. Bean. Dr Bean received her undergraduate degree in Mathematics and Biology from Murray State College, her MPH in Biostatistics from University of Michigan and her PhD in Biostatistics from the University of Texas at Houston. Dr. Bean was recruited from the University of Miami where she was Professor of Epidemiology and Public Health. Formerly she was the Chairperson of the Department of Biostatistics and Epidemiology at the University of Oklahoma and Director of the Biostatistics Core for the SCOR Center and Professor of Biostatistics at the University of Iowa. At all of these institutions she was extremely active in undergraduate and graduate student teaching in biostatistics. She also had extensive experience interacting with M.D. and Ph.D. investigators. At Cincinnati, she has developed a Biostatistical Core for the Children' s Hospital. She performs several important functions for the GCRC: 1. She reviews all protocols submitted to the SAC for appropriateness of design and statistical analysis. She interacts directly with investigators to ensure that protocols are modified in accordance with standards (included in the protocol submission packet for the GCRC) set forth by the SAC for biostatistical analysis. 2. She provides consultative services during the development of GCRC projects. We encourage investigators to obtain statistical consultation during the development of their projects to ensure there is optimal design to answer the research question. 3. She coordinates the curriculum regarding biostatistical analysis and data management for the Introduction to Clinical Research Module and provides additional presentations for the Topics in Clinical Research Series. She serves as a resource person for the Bioinformatics Core. Together with Cathy McGraw and John Pestian in the Informatics Core, Dr. Bean provides a valuable resource for help with data management.

10. Informatics Core

The Children' s Hospital Research Foundation (CHRF) has made a significant commitment to developing the Division of Pediatric Informatics (DPI). This new division is directed by John P. Pestian, Ph.D. It is responsible for conducting its own bio and health informatics research and is also responsible for collaborating with other clinical and basic science investigators by providing computing and data management expertise to CHRF' s 200 faculty and their staff. Prior to coming to Cincinnati, Dr. Pestian created and directed a web-base, Oracle database for managing all health encounters at all public schools in the state of Virginia (Welligent).

11. Perinatal Biology Training Grant

A major strength of the Division of Neonatology/Pulmonary Biology is the research infrastructure for basic and clinical sciences at the Children's Hospital Research Foundation (CHRF). This scientific base is further strengthened by the strong ties and close proximity of the Medical School and University of Cincinnati. The research labs of the CHRF are in a 7 story research tower that has 409,000 sq. feet of research space and 73,000 sq. feet for animal facilities. A new addition to the building opened in 1998, and a second new addition providing 112,000 sq. feet more research space will open in the fall of 2000. This building is a state of the art facility that houses all lab based research for the Children's Hospital as well as the Department of Molecular and Developmental Biology, a basic research department with distinguished PhD faculty. Molecular and Developmental Biology recruited Christopher Wylie, PhD, as Director and is expanding to emphasize the identification and analysis of genes that regulate development. A Center of Excellence in Molecular Biology of the Heart and Lung awarded by NHLBI from 1984 to 2000 to the University had as participants several faculty from Neonatology/Pulmonary Biology. This program significantly upgraded the infrastructure for molecular and transgenic mouse research at CHRF. Ongoing efforts to maintain a state of the art molecular research facility are demonstrated by institutional support for the development of core facilities for informatics, functional genomics and proteomics. Other programs that strengthen the general research environment at CHRF are a MD/PhD training program established in 1987 at the University of Cincinnati School of Medicine that is directed by Dr. Leslie Myatt in the Department of Ob/Gyn. The faculty listed on this training grant have been advisors for 3 successful MD/PhD. The graduate program in Molecular and Developmental Biology was established at the University of Cincinnati School of Medicine in 1971. Graduate students from this program presently work in the Neonatology/Pulmonary Biology labs. Graduate students from the Depts. of Cell Biology, Neurobiology and Anatomy also have trained in the Pulmonary Biology labs. The important concept is that the Neonatology/Pulmonary Biology research activities are integrated into a rich research infrastructure at CHRF and the University that provides all levels of training and complete facilities for basic research.

Although many of the mentors and associate mentors for this training grant have independent grant support, there are a number of programatic activities that strengthen the integration of research activities in Neonatology/Pulmonary Biology. Dr. Jeffrey Whitsett is the Director of a specialized center of research (SCOR) from NHLBI titled Pathobiology of Lung Development. The research projects range from studies of the genes and transcription factors regulating lung development to a clinical project that has characterized the genetic basis for a number of causes of respiratory failure in the newborn. Dr. Alan Jobe is the Director of a Program Project Grant on Surfactant Homeostasis in Health and Disease. This research emphasizes the use of transgenic mouse models that either lack or overexpress selected surfactant proteins or have regulatory abnormalities of the surfactant system. These programatic grants provide core facilities for histopathology, confocal microscopy, in situ morphology, lung physiology, and transgenetic technology that strengthen the overall research of the division. A targeted training program for clinical research training in neonatal/perinatal medicine also has been developed for fellows interested in formal training in clinical research. The clinical research environment is strengthened because the neonatal units at CHMC are participants in the NICHD Neonatal Research Network, with Dr. Ed Donovan as Principal Investigator. The obstetric units also are members of the Perinatal Research Network supported by NICHD.

12. FACILITIES AVAILABLE

General Facilities: All facilities within the University of Cincinnati Medical Center are available to Network activities. These resources include the College of Medicine, University Hospital and the Children's Hospital Medical Center. Although investigators in this program function primarily with the Department of Obstetrics, Pediatrics, Physiology, and Medicine, faculty in other departments - including Molecular Biology, Biochemistry and Microbiology, Psychology, Pathology, Physiology and Cell Biophysics, Anatomy and Cell Biology, and Environmental Health, are available on a day-to-day basis to provide consultation services and specialized equipment.

The new 8-floor, 120,000 square feet Pediatric Research Tower of the Children's Hospital opened in 1991. Sixty percent of the Perinatal Research Institute Faculty have space in this new facility which demonstrates the commitment of the Medical Center to Perinatal Research.

Clinical Facilities: Facilities for patient care at the University of Cincinnati Medical Center include the newly renovated labor and delivery areas and the Regional Perinatal Center at the University Hospital, the

Newborn Nurseries and the Neonatal Intensive Care Unit within the University Hospital, the newly constructed Regional Center for Newborn Intensive Care Unit at the Cincinnati Children's Hospital, the new Neonatal Intensive Care Unit at Good Samaritan Hospital and Level II Perinatal Units at Christ Hospital and Bethesda Hospital.

Newborn, Nurseries, University Hospital, Christ Hospital

The University Hospital and Christ Hospitals (members of the Alliance Network) have approximately 7,000 deliveries per year. Of these deliveries, approximately 12% involve low birth weight infants (birth weights below 2500 gm). The University Hospital provides care for a high-risk population comprised of medically indigent and high-risk referral obstetric patients. Every year, 450 infants are admitted to the Neonatal Intensive Care Nursery. The average daily census is 30 with personnel and facilities for intensive and sophisticated newborn care. The NICU at University Hospital is a spacious 23,000 square feet (17 foot ceiling) facility that accommodates 50 patients with possible expansion to accommodate 70 patients. This NICU provides ultramodern state-of-the-art technology and facilities. Located in the NICU is a neonatal pharmacy, neonatal radiology facility, numerous breast feeding rooms, dedicated "home style" family rest and living quarters, lounges, and a sibling play area.

Regional Center for Newborn Intensive Care, Children's Hospital Medical Center

The Regional Center for Newborn Intensive Care (RCNIC) at Children's Hospital accepts transfers from all newborn nurseries within a 50-75 mile radius and frequently (10%) from beyond. This provides a population base of 25,000-30,000 deliveries per year, with over 600-650 admissions per year. The average census is 35 infants (maximum 55 infants), with facilities and personnel for newborn care of all degrees of complexity include ECMO, high frequency oscillatory ventilation and inhaled nitric oxide.

Outpatient Services, Children's Hospital Medical Center

Follow-up evaluations of newborn infants discharged from the nurseries are performed in a special follow-up clinical in the Outpatient Department of Children's Hospital, or in the Clinical Research Center for specialized study protocols.

The Neonatal Intensive Care Unit and The Seton Perinatal Center at Good Samaritan Hospital

With over 5,000 annual deliveries and 700 annual NICU admissions to its state-of-the-art facilities, this is one of our busiest academic NICU's. Newborns are transported to Children's for ECMO, complex pediatric surgery, cardiac surgery and neurosurgery. All other NICU procedures including imaging, HFOV, PDA ligation, central catheter placement and subspecialty consultation/care are provided in-house.

OFFICES AND LABORATORY RESOURCES

Joint Division of Neonatology/Pulmonary Biology

The Division of Neonatology is located in the $50,000,000 University of Cincinnati Medical Center Building in a 13,000 square-foot area, and in the Children's Research Tower (13,700 square feet) which includes offices, conference-lecture facilities, and 16 laboratories. Available laboratory equipment in the Division includes 3 gamma and 2 beta scintillation counters; a mini-computer with computer terminals linking the Division to the University's large computer system; several IBM AT personal computers; polygraphs capable of measuring multiple physiologic variables; floor and table-top centrifuges; 3 Radiometer ICAI for measuring iCa; atomic absorption analyzer; spectrophotometers; 4 bone mineral analyzers; ultracentrifuges; in vitro organ perfusion equipment; Abbott auto-analyzer 100; 4 HPLC units with autosamplers and fraction collectors; column chromatographic and gel-electrophoretic equipment; DNA thermal cycler PCR machine; dual chamber automatic C02 incubator; luminescence spectrophotometer system; thermal imaging radiometer; thermogram image processing system; small animal incubator; blood gas analyzer; tissue and cell culture facilities including hood, incubator and refrigeration and sterile facilities; and 3 Formas deep freezers (-80), freezers and refrigerators, fine balance,balance, Pipet system, and International low speed centrifuge.

The Pulmonary Biology facility includes equipment for most common molecular biology procedures including DNA sequencing, PCR amplification, facilities for bacterial growth plasmid preparation, storage of restriction enzymes, nucleotides, vectors, bacterial and phage strains and libraries, etc. Mammalian cell lines used for transection, e.g., Cos, CH0, 3T3, and HeLa cells will be maintained. Facilities for electroporation, ultra-centrifugation, electrophoresis and oligonucleotide synthesis and purification will be provided. Equipment includes DNA sequencing equipment, electrophoresis, power sources, refrigeration and storage,

ultracentrifuge, a computer facility with updated data bank access and an olginucleotide synthesizer.

Regional Perinatal Center. The University Hospital's Regional Perinatal Center is located on the second floor of the Ambulatory Building, which is adjacent to University Hospital. There is 13,000 square feet of space which includes 14 examination rooms, a large reception and waiting room, consultation rooms, an ultrasound division, an antepartum testing unit, and a fetal echocardiography division. Equipment is available for routine obstetrical care and testing, specimen collection and immediate blood glucose analysis, and specialized diagnostic/surveillance/amniocentesis sonography. The Perinatal Center employs 1 Manager, 3 full-time R.N.'s, 6 Registered Diagnostic Sonographers, 3 Clerks, 1 Secretary, 1 Medical Assistant, 1 Dietician and 1 Financial Counselor.

University Hospital Obstetrical Services. The Maternal-Fetal Medicine Division have staffed the Obstetrical Special Care Unit at University Hospital on a 24-hour a day, 7 day a week basis. The physical presence of a perinatal faculty or fellow on the Obstetrical Special Care Unit provides assurance that the quality of care to mother, fetus and the newborn infant will remain at a very high level. This system of coverage was implemented to ensure compliance by our resident and nursing staff to clinical and research protocols in effect on the perinatal services.

Regional Perinatal Outreach Program. The Perinatal Outreach Program provides an unusual perinatal program that coordinates perinatal services throughout the city and community. Maternal-Fetal Medicine and Neonatology consultants are assigned to every hospital in the region, providing liaison and coordinated consultation services throughout the community. Regular morbidity and mortality conferences at area hospitals are attended by University/Children's perinatal/neonatal faculty, and citywide perinatal conferences are held at the University and Good Samaritan Hospitals. The degree of cooperation is unique for the country and reflects a long tradition of community interest in perinatal care.

Obstetrics Office and Laboratory Resources. The Department of Obstetrics and Gynecology is located in the Medical Sciences Building. It occupies 12,784 square feet of space devoted to office, laboratories, and conference/lecture facilities. Laboratories include walk-in cold and freezer rooms and small and large animal operating rooms. In addition, the perinatal ovine colony is housed in a separate building where there are facilities for holding, care, recovery, observation, and acute and chronic manipulation of ewes, lambs and sheep fetuses. Available equipment includes several multichannel analog recorders; a wide variety of electronic test equipment; spectrophotometers; a scintillation counter; apparatus for gas, liquid, thin-layer and paper chromatography; and other equipment required for fully equipped biochemistry laboratories.

Obstetrical Research Laboratories on the fourth floor of the College of Medicine have the following equipment available for use on this project:

1. Beta Couters - Packard 400 CD and Packard 1900 Ca
2. Gamma Counter - Packard 5000 Auto Gamma Counter
3. Autoclave
4. Beckman DU 65 Spectrophotometer
5. Waters 660 Solvent Programmer plus two Waters 600 AHPLC Pumps
6. Waters 490 Multiwavelength HPLC Detector
7. Schoeffel GM 970 HPLC Fluroescence Monochromator
8. Bas LC-4B HPLC Electrochemical Detector
9. Spectra Physics 8700 HPLC System
10. Fisher Series 5000 Recorders
11. Hewlett Packard 3390A Integrators
12. Pharmacia Frac 100 Fraction Collectors
13. Brinkman SC/4812 Sample Concentrator
14. Savant Vacuum Centrifuge
15. Beckman L7-75 Ultracentrifuge J2-21 Refrigerated Centrifuge
16. Beckman TJ-6 refregerated Bench Centrifuge
17. Vitris Freezemobile Freeze Dryer
18. Bioteck Instrument Microplate Reader
19. Baker 36-400 Sterilgard Laminar Flow Cabinet
20. Olympus CK2 Inverted Microscope

21. Zeiss Fluorescence Microscope
22. Two human placental perfusion systems with on-line 02 and pH monitoring and data collection and analysis on IBM PS/2 systems using Asystant Plus Software.

Perinatal Obstetric Research Core Laboratory has available:

1. Radiometer BMS-3 MK II Blood Gas Analyzer
2. Lex 02 Con TL Oxygen Content Analyzer
3. While blood/Plasma-Yellow Springs Model 23A Glucose Analyzer (Glucose Oxidase Method)
4. Yellow Springs Model 27-Industrial Analyzer (Lactate Oxidase Method)
5. Elmer Atomic Absorption Spectrophotometer
6. Buchler-Cotlove Chloridometer
7. Advanced Instrument Osmometer (Freezing Point)
8. Kanuer Membrane Osmometer
9. Beckman centrifuges
10. A vacuum centrifuge
11. A sample concentrator
12. pH meter
13. Beckman 3500
14. Mettler Balance
15. Two complete Phipps and Bird Isolated tissue baths
16. Two DMP-4A Physiograph with Grass stain gauge couplers
17. Isolated Cotyledon Sheep Placental Perfusion Apparatus with Accompanying Equipment
18. Gilford 250 Spectrophotometer
19. Health Dual Trave Oscilloscope Model SO-4450, Model ICA 1
20. Radiometer Flow through Calcium Ion Electrode
21. A Varian AA-1475 Atomic Absorption Spectrophotometry Unit available in Pediatrics

The GCRC at the Children's Hospital :

The GCRC provided more than $35,000 in support of 5 different Neonatal Research Network studies over the last five years.

History

In 1963, an NIH funded GCRC was established at the Children's Hospital. Initial construction costs of $239,719 were provided from support from the Children's Hospital Research Foundation and the National Institutes of Health. This was the fourth free standing Pediatric CRC funded by the NIH. It was directed by Wm. K. Schubert and was geographically and fiscally separate from the GCRC at the Cincinnati General Hospital. In 1979, Dr. Schubert became Chairman of the Department of Pediatrics and John C. Partin, was named Program Director of the Clinical Research Center. In 1981, George Hug became the Program Director. A renewal application, submitted in 1986, was approved but not funded. A reapplication was again approved but not funded. National Institutes of Health funding ended for the Children's Hospital GCRC in June 1989. However, between June 1989 and December 1, 1993, the Clinical Research Center was maintained intact and continued to function, supported by funds ($1,042,354) from the Children's Hospital Research Foundation. During this time, the CHRF renovated the existing GCRC and expanding it from 4400 sq feet to 8,800 sq feet at a cost of $1,005,000.

In 1991, plans were made to form a joint CHMC-University of Cincinnati GCRC with shared program direction between the two institutions. The intent was to reduce duplication between the two centers while assuring access to the resources needed for clinical research and a critical mass of investigators for cross-fertilization of ideas. Both inpatient and outpatient studies in both adults and children were then concentrated in the recently renovated facility at Children's Hospital. To keep the budget as lean as possible, resources apart from the center would be limited to scatterbeds for those studies that absolutely had to be conducted in the University Hospital, for either medical or logistic reasons.

In 1992, an application for a new GCRC at Children's Hospital as a joint University of Cincinnati-CHMC GCRC with the inpatient/outpatient facility at the Children's Hospital and scatter beds for adults at the University Hospital was submitted. Initial funding began on December 1, 1993. During this first 3 year cycle of funding, the CHMC renovated an outpatient area adjacent to the GCRC for use for research and clinical care at

a cost of $500,000 and providing 3,969 square feet additional space. Subsequently, the GCRC grant was successfully renewed for a 5-year period. The current funding includes support for the inpatient/outpatient units at the Children's Hospital, ancillary staff support including nurses, bionutritionists, biostatistician, Core Lab technical staff, and administrative staff. No inpatient or outpatient services are provided at the University of Cincinnati since the reviewers recognized that the vast majority of usage of the unit was from pediatric investigators and that the unit effectively was a pediatric CRC. In June 1999, a supplemental application was funded for the development of a Tissue Procurement Facility located in the Medical Sciences Building of the College of Medicine as a portion of the GCRC grant. The current funding cycle for the GCRC ends November 30, 2001.

Since its inception in 1964, investigators at the GCRC at the Children's Hospital have published a total of 917 journal articles and book chapters published relating to human studies conducted at the Center. Outstanding contributions have been made in a number of areas including seminal work leading to improved understanding of Reye's Syndrome and its pathogenesis, glycogen storage diseases, pediatric liver diseases including the delineation of a number of new inborn errors of bile acid metabolism, bone metabolism in health and disease in children, and lactating women, bile acid metabolism in infants and children, Gaucher Disease, hypertension in children and growth and development in white and black children, adolescents and young adults. A representative bibliography maybe found on Accomplishments, which represents accomplishments from the Center over the last 5 years.

Outstanding Core Laboratory that serves as a nidus for research. The Core Laboratory has moved from the Medical Sciences Building at the College of Medicine to the 4th floor above the GCRC. This move has led to enhanced lab/investigator interaction and provided a strong support for investigators in bone and body composition. During the last funding cycle, we purchased a new DEXA 4500A with monies solicited by the Development Office of the Children's Hospital. The CHRF also has purchased a pQCT for measurement of peripheral bone density. This instrument complements the existing 2 DEXAs. Usage of both the analytic lab and the body composition has been extremely strong leading to a number of important observations. Since the last application we have received supplemental funding (April 1999) for a Tissue Procurement Facility located in the Medical Sciences Building of the College of Medicine. This facility will serve to obtain tissues during surgical procedures and provide the opportunity for basic and clinical scientists to correlate clinical findings with tissue alterations. This is one of only 2 such facilities sponsored by the NCRR.

I. INTRODUCTION

The Division of Neonatology of the University of Cincinnati Medical Center (UCMC) is applying to continue to be a part of the NICHD Neonatal Research Network. We feel that we can provide a broad-based and expanding resource, relating to the following major points. Our Neonatal Intensive Care Unit (NICU) admission rate (all 3 NICU's) averages approximately 1850 NICU admissions per year including 380 annual admissions with birth weights less than 1500 grams. Two of our 3 NICU's, University Hospital and Children's Hospital, are within 5 minutes walk of each other. Our third NICU at Good Samaritan Hospital is approximately 1 mile from Children's Hospital. These 3 NICU's are the only NICU's serving the greater Cincinnati region (9,544 square miles and 30,000 annual births). A single Division of Neonatology/Pulmonary Biology under Dr. Jeffrey Whitsett, provides clinical and administrative services for each of the three NICU's. All 3 NICU's participate in clinical research directed by the Division of Neonatology/Pulmonary Biology. The two inborn units, University Hospital and Good Samaritan Hospital account for 7,500 deliveries per year or 25% of regional births and nearly all predictably identifiable regional high risk births. Cincinnati is unique in perinatal care because the metropolitan and surrounding rural areas (9,544 square miles) are integrated through a longstanding and successful **Perinatal/Neonatal Outreach Network**. This network of all 17 regional obstetrics hospitals has maintained, since 1982, a **Regional Perinatal Database** which contains all regional live births, fetal deaths and neonatal deaths by race, birth weight category and presence or absence of a lethal malformation. Regional Perinatal Statistics are summarized in the following table:

LIVE BIRTHS, ALL REGIONAL HOSPITALS					
	1995	**1996**	**1997**	**1998**	**1999**
less than 2500 gms	2127	2046	2096	2239	2437
less than 1500 gms	412	402	385	465	504
TOTAL	28724	28374	28804	29255	30025

With our current five Network Research Nurses, plus additional resources generated by enrollment in Network studies and the scatterbed/nursing resources of our GCRC, we efficiently cover Network activities at each of the 3 participating hospitals. **This large pool of clinical material at the University of Cincinnati, in addition to our strong GCRC, our Investigative Pharmacy and our strong history of collaborative, clinical research, greatly strengthens our ability to contribute to Network studies.**

Over the last 2 1/2 years, 91% of all infants (761 of 837) in our region with birth weights <1500 grams (VLBW) were cared for by UCMC neonatologists at one of the 3 participating NICU's. Most of the VLBW infant's remaining at level II hospitals were also cared for by our neonatology group. All neonatologists in the region are part of one Division of Neonatology. There are efficient maternal and infant transport systems that bring high risk mothers to University Hospital or Good Samaritan and all sick outborn newborns to 1 of the 3 NICU's (over 90% are transported to Children's Hospital Medical Center).

Our commitment to research is attested by the large number of NIH grants with individual faculty members as principal investigators and with groups of investigators, such as Program-Project Grants and Center grants.

Our facilities for care are superb; and we have excellent risk-adjusted clinical outcomes. We have recently occupied, new, ultra-modern and sophisticated, fully computerized NICU's: University Hospital in 1990, Children's Hospital Medical Center in 1993, and Good Samaritan Hospital in 2000.

Our collaboration with the Division of Maternal-Fetal Medicine is fully operative and substantiated by a long standing track record of collaborative research and training, including a concurrent renewal application in the Network of Maternal-Fetal Medicine Units.

Cincinnati has one of the largest neonatology training fellowship programs in the country: nearly 100 fellows have been trained, and approximately 60% have continued in academic neonatology; 11 are currently in training. An NIH Perinatal Biology Training Program has been in place for the last 23 years.

Our group of exceptionally talented, often internationally renowned, neonatologists is large (n = 20) and unanimously committed to the concept that the most important and controversial issues of neonatal care can best be addressed by carefully planned and conducted, prospective clinical trials. This group of neonatologists is fully supportive of this application and the commitment that it entails (see letters of support in Appendix A). Institutional commitment to clinical trials and epidemiologic research is exemplified by our strong Biostatistics and Epidemiology Departments and Perinatal Research Institute Biostatistics and Epidemiology Section, by the number of neonatology studies supported by our GCRC, by the creation of a Child Health Statistics Center directed by Dr. Donovan and by the recent establishment of a Clinical Trials Fellowship in Pediatrics. Cincinnati has an excellent track record of clinical trials in neonatology, both within the UCMC system and in collaboration with other centers.

Pediatric Pharmacology Research Unit (PPRU):

In response to the need for appropriate drug therapy for pediatric patients, the National Institutes of Child Health and Human Development (NICHD) established a network of Pediatric Pharmacology Research Units (PPRU). Cincinnati Children's Hospital Medical Center has been selected by the NICHD as one of 13 participating units located throughout the United States. The network contains 160,000 pediatric inpatients a year and 2.3 million outpatient pediatric contacts per year. The mission of PPRU network is to facilitate and promote pediatric labeling of new drugs or drugs already on the market. The PPRU laboratory capabilities include: gas chromatography (HP6890 GC with FID and NPD detection), high performance liquid chromatography (two thermo separations HPLC's with UV, fluorescence, and electrochemical detection), various immunassays (radioimmunoassay; enzyme immunoassay; fluorescence polarization immunoassay; and microparticle enzyme immunoassay), polymerize chain reaction, LC-MS and GC-MS located in the Clinical Mass Spectrometry Center.

CHMC Office of Clinical Trials:

This newly formed program was established to coordinate and facilitate all clinical trials performed by Children's Hospital Medical Center faculty and staff. Because of the unique developmental, behavioral and legal status of children, clinical research is ethically, practically, and scientifically more difficult to perform in children than in adults. In addition, the rapidly changing legislative environment has simultaneously created increased volume of clinical trials at the same time as the regulatory requirements for such trials have become more complex. In addition there is a growing shortage of adequately trained clinical investigators and increasingly concern over real or potential conflicts of interest and commitment on behalf of investigators. Non-profit academic institutions are also faced with increasingly difficult problems. They must guarantee that grants and contracts with for-profit corporate sponsors maintain both scientific credibility and fiscal responsibility. Academic centers must not become perceived as being "purchased" by industry and must be sure that all contracts maintain academic freedom and scientific objectivity. Contract research must be fiscally responsible to make sure that grant and contract budgets are fiscally responsible and do not result in subsidization of a for-profit entity. In addition, federally funded academic institutions must conduct clinical trials according to strict federal guidelines or risk losing all federal finding, not just clinical trials funds. In addition, federal guidelines for conducting clinical trials are becoming more complex at the same time that federal enforcement of these guidelines is becoming more intense. The Office of Clinical Trials was established as a resource for CHMC faculty and staff to help them obtain and conduct scientifically important, ethical clinical trials in a way which is fiscally responsible and conforms to all regulatory requirements. The Office of Clinical Trials is headed by a physician (P.Walson, MD) who is a tenured Professor of Pediatrics, board certified in pediatrics, clinical pharmacology, and medical toxicology with over 27 years' experience conducting pediatric clinical trials.

UCMC Office of Clinical Trials (http://www.clinicaltrials.uc.edu)

In concert with the Clinical Trials Office at the Children's Hospital Medical Center, the Office of Clinical Trials at the University of Cincinnati Medical Center will provide further support for all research protocols conducted in the NICUs. This centralized administrative unit directed by Loren Friedman, M.S. has been established to serve the needs of clinical investigators who conduct clinical research sponsored by both the government and the pharmaceutical industry. It serves as a primary point of contact for private sector and government sponsors seeking to select a site for their trials, as well as for investigators seeking external funding

for their own initiated protocols. The goals of this office are to stimulate the quality and quantity of clinical trials; to streamline the research process, from protocol design to publication; and to educate investigators in Good Clinical Practice, Regulatory Affairs and Study Management.

II. ACADEMIC PRODUCTIVITY

A. Contributions to NICHD Neonatal Research Network productivity:

Since joining in 1991, the University of Cincinnati has contributed significantly to the productivity of the NICHD Neonatal Research Network. We have been an **active participant in all Network studies** while taking **leadership roles in the Ballard study** (training of Network research nurses by Dr. Jeanne Ballard and Dr. Donovan serving as Chair of Ballard Subcommittee), the **Vitamin A ROP secondary study (Dr. Donovan PI), Twins study (Dr. Donovan PI) and the recently initiated Surfactant-CPAP trial (Dr. Donovan PI). Dr. Donovan is currently serving on the following Network committees: Publications (Chair), Hypothermia, Sedation, Cord Clamping Pilot, Surfactant/CPAP (Chair) and formerly served on Ballard (Chair), Dexamethasone, EPO, Growth, SAVE, and GDB subcommittees. The University of Cincinnati has served as the Network's Central Investigative Pharmacy** for distribution of study drugs. Cincinnati actively participated in **development of the Network follow-up** activities and in the **development of materials** for communicating Network activities to parents and staff (see Appendix B). We have initiated or participated in several **multiple Network ancillary studies** (see Appendix C). Our **recruitment and study consent rates** in proportion to the size of our patient population are among the best in the **current Network (see Appendix D for Network 1995-2000 publications in which Cincinnati participated).**

B. Summary of Cincinnati participation in NICHD Neonatal Research Network studies:

1. Generic Database:

The Network's Generic Database (GDB) is a registry of descriptive, risk-related and outcome data for all Network VLBW infants (401-1500 grams birthweight). These data characterize infants admitted to Network NICU's, allow examination of the relationships between selected risk factors and outcome, allow description of trends in incidence of selected morbidities and mortality and provide the basis for building hypothesis for future multi-center studies. Since joining the current Network in April 1, 1995 through May 31, 2000, all 1739 eligible Cincinnati infants have been enrolled.

GDB by gender and race and hospital 1999

University Hospital

1-1-99 to 12-31-99	Black N (%)	Hispanic N (%)	White N (%)	Other N (%)	Missing N (%)	Total
	57 (42)	0 0	78 (57)	(<0.1)	0 (0)	136

Children's Hospital Medical Center

1-1-99 to 12-31-99	Black N (%)	Hispanic N (%)	White N (%)	Other N (%)	Missing N (%)	Total
	11 (26)	1 (2)	31 (72)	0 0	0 0	43

Good Samaritan Hospital

1-1-99 to 12-31-99	Black N (%)	Hispanic N (%)	White N (%)	Other N (%)	Missing N (%)	Total
	46 (24)	2 (1)	138 (73)	2 (1)	0 0	188

GDB annual enrollment

1996	1997	1998	1999
350	324	386	367

2. A Multicenter, Randomized Comparison of the Efficacy and Safety of Early versus Late Dexamethasone for the Treatment of Chronic Lung Disease of Premature Infants (NEJM 338:1112-1118, 1998).

	Number screened	Number eligible	Number (%) randomized	Network centers mean % eligible	Network centers mean % randomized
8/92 to 6/95	160	55 (34.3%)	**31 (56.3%)**	27%	62%

3. Development of Standards for the New Ballard Score (J Pediatr 135(2):147-152, 1999).

	Number Screened	Number Eligible (%)	Number Enrolled (%)	Number gold standard (%)	Network centers mean % gold standard
6/94 to 3/96	275	245 (89%)	198 (81%)	23 (12%)	20%

4. Observational Study of Growth of VLBW Infants (Pediatrics 104(2):280-289, 1999).

	Number Screened	Number Eligible (%)	Number Enrolled (%)
10/94 to 8/95	114	93 (82%)	93 (100%)

5. Randomized Neonatal Inhaled Nitric Oxide Study (NINOS) (NEJM 336:597-604, 1997).

	Number screened	Number eligible (%)	Number randomized (%)
9/95 to 5/96	9	8 (89%)	**7 (88%)**

6. Randomized Trial of Vitamin A Supplementation for Extremely-Low-Birthweight Infants (NEJM 340:1962-1968, 1999).

	Number screened	Number eligible (%)	Number enrolled (%)	Network % enrolled
1996 to 1997	134	85 (63.4%)	**57 (67.1%)**	65%

7. In Utero Magnesium Sulfate Exposure: Effects on Extremely-Low-Birthweight (ELBW) Infants

This was a prospective cohort study with 1,339 infants enrolled to ascertain whether in utero magnesium sulfate exposure is associated with a reduced risk of intracranial hemorrhage and or cerebral palsy. No effect was observed (Ped Res 1999; 45: 207A)

	Number Screened	Number Eligible	Number Enrolled
7/96 - 6/98	208	208 (100%)	**208 (100%)**

8. The Effects of Erythropoietin (EPO) on the Transfusion Requirements of Preterm Infants 401-1250 Grams: Two Multi-center Randomized, Double Masked Placebo Controlled Studies.

These were two trials in two different birth weight strata: 401-1000 and 1001 - 1250 grams. 650 infants were enrolled. EPO had little effect on transfusion requirements. Manuscripts are in preparation.

	Number Screened	Number Eligible(%)	Number Enrolled(%)	Network centers Avg. % Eligible	Network centers Avg. % Enrolled
10/97-7/98	71	47 (66%)	19 (40%)	75%	48%

9. Randomized Trial of Minimal Ventilator Support and Early Corticosteroid Therapy to Increase Survival Without Chronic Lung Disease in Extremely-Low-Birthweight Infants (SAVE)

This was a 2X2 factorial design trial in which the effects of permissive hypercarbia (unmasked) and early

stress dose glucocorticoid (masked) were simultaneously evaluated in infants 501-1000 grams birth weight. The study was halted by the Data Safety and Monitoring Committee after enrollment of 220 infants because of an increased incidence of gastrointestinal perforation felt to be associated with early glucocorticoid exposure particularly with concomitant indomethacin. (Pediatr Res 104:739, 1999, Pediatr Res 47(4):2310, 2000)

	Number screened	Number eligible	Number enrolled	Network % enrolled
5/98 to 9/98	19	14 (74%)	12 (86%)	65%

10. Follow-up Study of Infants Less than 1,000 grams Birth Weight:

The purpose of the Follow-up Study is to examine, at 18-22 months corrected age, infants in the Generic Database with birth weights 401-1000 grams. **Dr. Steichen of Cincinnati is co-Chair of the Network Follow-up Subcommittee.** This study was initiated at our center for all 401-1500 g survivors born after 12/31/92. Maximizing enrollment has been possible primarily due to our well established high-risk Infant Follow-up Clinic. Social workers are available in all 3 NICU's with established contacts with local county caseworkers, a well established Pediatric Primary Care Clinic, an Outreach coordinator, community health workers who can serve as a liaison for hard-to-track families and established relationships with community clinics and private pediatricians. The following table includes infants who have reached the 18-22 month window for the follow-up examination. The decrease in followup compliance seen 1995-97 was due in large part to the addition of the Good Samaritan Hospital cohort in September, 1995 and slow followup startup. Current followup rates are greater than 90% for Cincinnati infants as a group, ie all 3 participating hospitals.

YEAR of birth	Survivors 401-1000g Cincinnati	Survivors 401-1000g GSH	18-22 month visit Cincinnati	18-22 month visit GSH
1993	57	xxx	91%	xxx
1994	41	xxx	88%	xxx
1995	59	9 (9/95-12/95)	83%	78%
1996	116	52	75%	67%
1997	123	68	85%	90%
1st 6mo. 1998	58	23	91%	96%

11. A Multicenter Study of Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) (Pediatrics 105:14-20, 2000).

	Number screened	Number eligible (%)	Number enrolled (%)
5/94-3/99	Approx. 700	51 (7.3%)	26 (51%)

12. Early Inhaled Nitric Oxide (EINO) Study:

This is a randomized, masked trial of early inhaled nitric oxide in term and near-term infants with moderate (rather than severe as in the NINOS trial) hypoxic respiratory failure. Enrollment began September 1998 in some network centers and this trial is ongoing.

	Number screened	Number eligible	Number enrolled (%)
9/98-6/00	Approx. 300	5	4 (80%)

13. Randomized Trial of Parenteral Glutamine Supplementation for Extremely Low Birth Weight Infants:

This is a randomized masked trial of supplemental parenteral glutamine to reduce the incidence of nosocomial infection in infants 401-1000 grams birth weight. Enrollment began in the fall of 1999 and is ongoing.

	Number Screened	Number Eligible (%)	Number Enrolled (%)	All Network Centers Avg % Eligible	All Network Centers Avg % Enrolled
10/99-present	29	24 (83%)	21 (88%)	81%	71%

14. Randomized Controlled Trial of Induced Hypothermia for Hypoxic-Ischemic Encephalopathy

This is a randomized, unmasked trial of total body hypothermia to reduce the incidence of death or neurodevelopmental handicap in term and near-term infants with moderate-severe hypoxic ischemic encephalopathy. Enrollment in this study is ongoing. The University of Cincinnati center has screened one infant who was eligible and enrolled.

15. Early Surfactant Followed by Nasal CPAP to Reduce the Use of Mechanical Ventilation Without Additional Morbidity in Infants 1250-2000 Grams with RDS

This is a randomized unmasked trial of early surfactant followed by immediate extubation to nasal CPAP to safely reduce the use of mechanical ventilation in infants 1250-2000 grams birth weight. This trial is begins July 1, 2000 (Dr. Donovan is PI).

16. A Randomized Comparison of the Efficacy and Safety of Exosurf Neonatal and Survanta for the Treatment of Respiratory Distress Syndrome (J Pediatr 123(5):757-766, 1993).

	Number Screened	Number Eligible	Number Randomized	Network centers Avg. % Eligible	Network centers, Avg. % Randomized
7/91 - 1/92	96	46 (48%)	**35 (76%)**	46%	70%

17. Prediction of Significant Hyperbilirubinemia in Term Infants (Clin Chem 40:1934-1939, 1994).

	Number Screened	Number Eligible (%)	Number Enrolled (%)	Network centers Avg. % Eligible	Network centers Avg. % Enrolled
11/91-6/92	59	44 (74%)	12 (27%)	84%	46%

18. Antenatal Phenobarbital in the Prevention of Neonatal Intracranial Hemorrhage (NEJM 337:466-471, 1997)

	Number screened	Number eligible	Number randomized (%)	Network centers mean % eligible	Network mean % randomized
3/93 to 4/93	39	7 (18%)	**6 (85%)**	0.21	0.48
5/93 to 4/94	326	63 (19%)	**43 (69%)**	0.2	0.58
5/94 to 2/95	244	43 (17%)	**28 (65%)**	0.18	57%

19. Ancillary study: Effects of Antenatal Phenobarbital on Preterm Infant Physiologic and Behavioral Responses to Routine Procedural Care. Gail McCain, MSN, PhD, Director of Nursing Research, Children's Hospital Medical Center, Principal investigator (Res Nursing Hlth 22(6):461-470, 1999)

Phenobarbital ancillary	Number eligible	Number enrolled (%)
03 - 27 - 93 to 04 - 30 - 93	5	2
05 - 01 - 93 to 04 - 30 - 94	37	35 (94.5%)
05 - 01 - 94 to 02 - 17 - 95	17	15 (88.2%)

20. Observational Study of Persistent Pulmonary Hypertension (Pediatr 105:14-20, 2000)

	Number screened	Number eligible (NN01)	Number enrolled (NN02)
9/93 to 4/94	507	109 (21%)	18 (17%)
5/94 to 12/94	503	119 (24%)	27 (23%)

21. HUMAN SUBJECTS: A list of current, IRB approved, Neonatology clinical studies may be found in Appendix E.

22. University of Cincinnati Perinatal Multi-Disciplinary Research Programs are listed in Appendix H.

III. NEONATOLOGY AND MATERNAL-FETAL MEDICINE STAFF

A. Joint Divisions of Neonatology/Pulmonary Biology

The joint Division of Neonatology/Pulmonary Biology is responsible for the clinical care of neonates, teaching of fellows and residents, and research into neonatal disorders and their prevention. The sub-Division of Pulmonary Biology, established in 1987, is the Basic Science arm of the Joint Division. The Division of Pulmonary Biology section, headed by Dr. Jeffrey Whitsett, is the nucleus of molecular biology research. The Fetal and Neonatal Physiology Section is directed by Dr. L. Myatt and includes: C. Joiner of Neonatology, Drs. J. Cuppoletti and N. Sperelakis of the Department of Physiology and Biophysics, Drs. W. Larsen and R. Drake of the Department of Anatomy and Cell Biology, and Dr. M. Lieberman of the Department of Molecular Genetics, Biochemistry and Microbiology. The Perinatal Clinical Investigators' section and includes: Mr. H. Atherton, Drs. E. Donovan and S. Hoath of Neonatology, collaborating with Drs. T. Siddiqi, and B. Rosenn of the Department of Obstetrics and Gynecology, Dr. R. Buncher of Biostatistics, Drs. H.T. Henderson and J. Nevin of the Electrical Engineering Department and Dr. W. Heineman of the Chemistry Department. Perinatal research is an officially designated major focus area for the University of Cincinnati College of Medicine. We are in the 23rd year of our NIH Perinatal Research Training Grant, open to fellows in 10 disciplines interested in perinatal developmental biology.

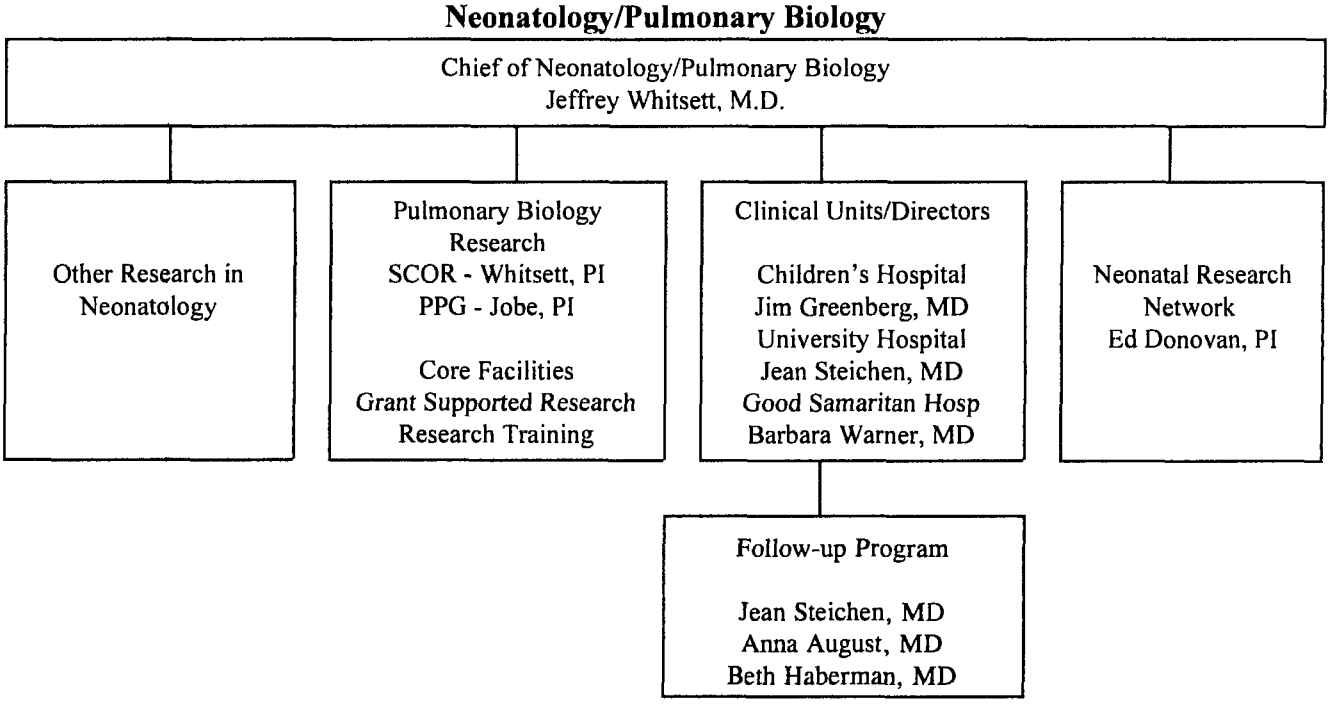
Dr. Jeffrey Whitsett is Director of the joint Division of Neonatology/Pulmonary Biology. Dr. James Greenberg is Director of the Regional NICU at Children's Hospital Medical Center and Dr. Jean Steichen is the Director of the Nurseries at University Hospital. Dr. Barbara Warner is Director of the Good Samaritan Hospital NICU. Dr. Donovan is liaison to Christ Hospital for neonatology services and Director of Regional Outreach which coordinates neonatal services in area hospitals. Dr. Jean Steichen is Director of the Follow-Up Clinics; Dr. Beth Haberman is the new Associate Director for Follow-up Research; and Dr. Ward Rice and Dr. Alan Jobe are Co-Directors of the Neonatal Fellowship and Training program. Dr. Jack Reuter is Chairman of the Regional Nursery Directors group. Division neonatologists are involved in patient care at nearly all major metropolitan perinatal facilities. Cincinnati is one of a few cities in the U.S. where regionalized perinatal and neonatal care exists. High risk pregnancies are referred to the University and Good Samaritan Perinatal Centers, and ill neonates are referred to Children's Hospital, thus optimizing use of community resources and minimizing health care costs for the region.

B. Research Highlights

The Division of Neonatology at University Hospital, Good Samaritan Hospital and the Children's Hospital Medical Center (CHMC) is composed of 36 full-time faculty members (20 M.D. neonatologists) and fellows. Most faculty members are M.D.'s and board-certified pediatricians as well as board-certified neonatologists. All members of this Division enthusiastically support this application (see letters of support in Appendix A). The faculty of the Division of Neonatology and their areas of research interest are listed below (those certified in Neonatal-Perinatal Medicine are indicated by an asterisk).

*Anna M. August, M.D.	Follow-up
Ann Akeson, Ph.D.	Pulmonary Biology
*Henry Akinbi, M.D.	Molecular Genetics
Cindy J. Bachurski, Ph.D.	Pulmonary Biology
Lynn Bertsch, RNC, MSN, APNN	Director, Neonatal Advanced Practice Nurse Program
*Kristina Bry, M.D., Ph.D.	Pulmonary Biology
Zissis C. Chroneos, Ph.D.	Pulmonary Biology
*Michael W. Crossman, M.D., Ph.D.	Developmental Gastroenterology
*Edward F. Donovan, M.D.	Clinical trials, health services research
*Horatio Falciglia, M.D.	Pathophysiology of meconium aspiration syndrome
*Jon H. Fridriksson, M.D.	Clinical Investigator, Therapeutics of PPHN
Stephen Glasser, Ph.D.	Pulmonary Biology
*James Greenberg, M.D	Hematopoietic stem cell regulation, Director, CHMC-NICU
*Okyanus Gurel, M.D.	Pulmonary Biology
*Beth Haberman, M.D.	Clinical Investigator, Developmental Follow-up
*Steven B. Hoath, M.D.	Skin Physiology
Machiko Ikegami, M.D., Ph.D.	Surfactant Physiology
*Alan H. Jobe, M.D., Ph.D.	Pulmonary Biology
*Suhas Kallapur, M.D.	Pulmonary Biology, Cytokines
Thomas R. Korfhagen, M.D., Ph.D.	Pulmonary Biology
Michael L. Mucenski, Ph.D.	Pulmonary Biology
*Vivek Narendran, M.D.	Skin Biochemistry-Physiology
*John H. Reuter, M.D., Ph.D.	Chair, Regional Nursery Directors
*Ward R. Rice, M.D., Ph.D.	Surfactant biochemistry, Dir., Neonatal Fellowship Training Program
John M. Shannon, Ph.D.	Pulmonary Biology
*Jean J. Steichen, M.D.	Behavioral Pediatrics; Director of Infant Follow-up Program
*Barbara Warner, M.D.	Basic mechanisms of pulmonary oxidant injury
Timothy Weaver, Ph.D.	Molecular Biology, Pulmonary Biology
*Kathy Wedig, M.D.	Behavioral Pediatrics; Good Samaritan Hospital
Susan E. Wert, Ph.D.	Pulmonary Biology
*Jeffrey A. Whitsett, M.D., Ph.D.	Molecular Biology; Director, Pulmonary Biology
Cong Yan, Ph.D.	Pulmonary Biology

The organization of the Neonatal/Pulmonary Biology division is given in the following figure.



C. Research interest details and selected publications of Neonatology faculty are included in Appendix F.

D. Collaborations Between Faculty: The strength of the Neonatology Division is that research ranges from molecular genetics and the production of transgenic mice to physiology and clinical research. To accomplish the research goals of ultimately applying biological research to clinical care, the group publishes collaborative research that integrates molecular technology with physiological outcomes. The general areas of collaborative research are listed below:

1. Generation of Transgenic Mice: Whitsett, Korfhagen, Weaver, Glasser, Rice, Greenberg
2. Study of SP-A Metabolism/Function in Knockout Mice: LeVine, Ikegami, Jobe, Korfhagen, Whitsett
3. Study of SP-B Function/Regulation/Knockout Mice: Weaver, Ikegami, Jobe, Akinbi, Wert
4. Study of SP-C Function/Metabolism/Regulation: Glasser, Weaver, Jobe, Ikegami, Bachurski, Korfhagen
5. Study of SP-D Function/Metabolism/Regulation: Korfhagen, Ikegami, Jobe, Whitsett, Wert
6. Lung Host Defenses: LeVine, Korfhagen, Trapnell, Akinbi, Bachurski
7. Promotors/Transcription Factors/Gene Regulation: Whitsett, Glasser, Weaver, Bachurski, Crossman
8. Regulation of Early Lung Development: Shannon, Whitsett, Rick Greenberg
9. Lung Maturation: Jobe, Ikegami, Bry, Bachurski, Shannon
10. Lung Injury, BPD: Bachurski, Bry, Jobe, Ikegami, Trapnell, Akinbi, Whitsett
11. Viral Vectors: Trapnell, LeVine, Weaver, Whitsett
12. Lung Cell Isolations: Rice, Weaver, Jobe, Ikegami, Shannon
13. Clinical Research: Donovan, Jobe, Wert, Whitsett, Akinbi, Hoath

E. The following is a brief description of the individual faculty members directly involved with this application.

Dr. Edward F. Donovan will serve as the Principal Investigator in the proposed grant application. Dr. Donovan currently serves as principal investigator for the Cincinnati portion of the NICHD Neonatal Research Network. He is chair of the Neonatal Network's Publication Subcommittee, co-chairman of the Surfactant/CPAP Subcommittee and serves on the Hypothermia, Sedation and Cord Clamping Pilot subcommittees. Dr. Donovan graduated from Stanford University, U.C.L.A. Medical School and completed his internship and pediatric residency at Children's Hospital Medical Center in Cincinnati. He completed a 3

year fellowship in newborn physiology at the University of Cincinnati College of Medicine and respiratory muscle physiology at McGill. Dr. Donovan is Professor of Pediatrics and is board-certified in Neonatal-Perinatal Medicine. He devotes approximately % of his time to clinical care, % to administration, and % to research. Dr. Donovan is an active clinical investigator, focusing in recent years on clinical trials (natural surfactant, Network trials, etc) and population-based, outcomes/health services research. He is Director of the University of Cincinnati's Child Health Statistics Center.

Dr. Barbara Warner will serve as co-Principal Investigator for the Cincinnati component of the NICHD Neonatal Research Network grant. Dr. Warner graduated from the University of Cincinnati College of Medicine and has an M.S. in Epidemiology from Amherst. She served as Research Instructor in the University of Cincinnati Department of Pediatrics from 1994-97 and is currently Research Assistant Professor of Pediatrics. Dr. Warner is Director of the NICU at Good Samaritan Hospital. Her research interests include basic science studies elucidating mechanisms of neonatal tissue injury. She is currently PI of an ancillary study to the Network glutamine trial evaluating the role of epidermal growth factor in the pathogenesis of necrotizing enterocolitis.

Dr. Beth Haberman is Associate Director of Research for the Cincinnati NICU developmental followup program. Dr. Haberman attended the University of Louisville School of Medicine. After Neonatal-Perinatal Medicine fellowship at the University of Cincinnati, Dr. Haberman joined the faculty of the Cincinnati Division of Neonatology/Pulmonary Biology. Her research interests are in long term neurodevelopmental outcomes of high risk newborns. At the May, 2000 Society for Pediatric Research meetings, she gave a platform presentation of a study that evaluated the presence of biased loss to followup in the NICHD Neonatal Research Network followup study (Ped Res 47(4):312A, 2000).

Dr. Jean J. Steichen received his medical degree from the Descartes Medical School at the University of Paris, France. **Dr. Steichen served as co-chair of the Network Follow-up Subcommittee.** He completed his internship and pediatric residency at the University of Cincinnati College of Medicine where he also did a 3 year neonatology fellowship. Following his fellowship, he joined the faculty at University of Cincinnati College of Medicine, Department of Pediatrics. In addition to his duties as Associate Professor of Pediatrics, Obstetrics/Gynecology, Dr. Steichen is the director of the NICU Follow-up Program at Cincinnati Children's Hospital Medical Center. He is board certified in Pediatrics and Neonatal-Perinatal Medicine. Dr. Steichen studies infant nutrition, bone mineralization and calcium and mineral metabolism in low birth weight infants. Dr. Steichen spends approximately % of his time with the Infant Follow-up clinic and is committed to devote % of his time to projects related to the Network.

F. Research Nurse Staffing

Currently the Cincinnati component of the Neonatal Research Network has five, dedicated Research Nurses. These include: Marcia Mersmann, RN, Clinical Research Coordinator (% FTE); Cathy Grisby, RN, Staff Research Nurse (% FTE); Barbara Alexander, RN, Staff Research Nurse (% FTE); Jody Shively, RN, Staff Research Nurse (% FTE); and Holly Mincey, RN, Staff Research Nurse (% FTE). Michele Boshko, BA is the Network Data Abstractor (% FTE). The combined Network Research Nurse experience totals 16 years. Additionally, Ms. Alexander had four years of research experience with the NIH Maternal Fetal Network prior to coming to the Neonatal Network in July of 1999.

The Cincinnati Network team stations one full time research nurse at each hospital responsible for all screening and enrollment into Network studies at that hospital, assisting coordinator with all aspects of coordination at that hospital, and being thoroughly acquainted with personnel and unit changes. This intimate connection between research nurses and the hospitals allows us to promptly initiate NIH studies. Since Ms. Grisby is our most experienced Research Nurse, she will provide back up at each hospital for times of increased census, high enrollment and during personnel illness and vacations. Research Nurse biographies may be found in Appendix G.

G. Maternal-Fetal Staffing

The M-FM Division at the UCMC is currently composed of 10 M-FM subspecialists comprising 6 full-time faculty and four affiliated faculty, the affiliated faculty being based at the GSH. There are also 4 Ph.D. faculty and 3 fellows-in-training in the M-FM Division. In addition, there are 5 full-time general obstetricians and gynecologists on faculty who provide obstetric care and actively participate in resident staff teaching and in-house

night-call. Eight of the 10 M-FM faculty are Board Certified in M-FM. The following is a brief description of key M-FM faculty members and their academic responsibilities and research interests:

Dr. Tariq A. Siddiqi, Professor and Director, Division of M-FM: Dr. Siddiqi, the Principal Investigator for the Cincinnati MFMU, is Professor (tenured) and Director of the Division of M-FM. He is also the Director of M-FM services for the Health Alliance of Greater Cincinnati as well as being the Director of Obstetrics at UHI. He has been in this administrative position since 1988, is board- certified in Ob/Gyn and M-FM and is also the Director of the M-FM Fellowship Program which has been in place at Cincinnati since 1976. Dr. Siddiqi chairs the Director of Obstetrics Regional Group and has served in city and state committees for improving perinatal care. He serves on UCMC College of Medicine and UHI committees focused around perinatal and womens' health.

As Division Director and Chief of Obstetrics, Dr. Siddiqi supervises the key faculty, support personnel and laboratory services relevant to the proposal . He possesses excellent organizational abilities and has a proven track record as a researcher and clinician. Dr. Siddiqi's expertise lies in the areas of obstetric ultrasound and its bioeffects and clinical perinatology. He has received continuous extramural research support since 1987. He has been a member of the American Institute of Ultrasound in Medicine Bioeffects Committee since 1992 and has chaired this Committee from 1997-1999, the only MD member to ever chair this committee. He is a member of the Board of Trustees of the National Perinatal Association.

Dr. Siddiqi has served as the Alternate Principal Investigator for the Cincinnati MFMU since 1990 and is very familiar with the workings of the MFMU Network. Since Dr. Miodovnik's departure from Cincinnati, he has assumed the responsibilities of the Principal Investigator and has assured a smooth transition. He has previously submitted several concepts to the Steering Committee as noted in Section B, page 10. He has considerable experience with multidisciplinary trials and was the Principal Investigator for the Clinical Core of the Program Project Grant: "Cell Biology of the Myometrium in Term and Preterm Labor". He participated in the multicenter national trial funded by the HHS: "Therapy, Basic Studies, Outreach Programs in HIV", the "Fetal Alcohol Syndrome: Prevention Research Program" and the R.W. Johnson: "A Double-Blind Placebo Controlled Safety and Efficacy Study of Antocin® for the Prolongation of Gestation" and was the Principal Investigator for the Clinical Trial: "Prevention of Intrauterine Growth Retardation by Bed Rest" which was part of the NIH Perinatal Emphasis Research Center (PERC) award.

As Principal Investigator of this application Dr. Siddiqi will devote % of his time to the proposed project. He will attend all Steering Committee meetings and be responsible for proper implementation of selected trials at the UCMC. This will include recruitment and management of patients as specified in the protocols, and accurate collection and transmission of research data.

Dr. Baha M. Sibai, Professor and Director, Department of Obstetrics and Gynecology: Dr. Sibai is the Alternate Principal Investigator for the MFMU Network at the UCMC after serving as Principal Investigator at the University of Tennessee at Memphis for 15 years. He came to the UCMC in May, 2000 as the Director of Ob/Gyn. Because of his involvement in the MFMU Network since its inception, Dr. Sibai is committed and familiar with all aspects needed to ensure future success of the NICHD MFMU Network.

Dr. Sibai is a national and international authority regarding preeclampsia and eclampsia and has published extensively using data from the MFMU Network between 1995 - 2000 (see biographical sketch). During the past years, Dr. Sibai has designed and completed clinical trials dealing with the use of labetalol in the management of preeclampsia remote from term, the use of nifedipine in the management of preeclampsia remote from term, a randomized trial comparing aggressive versus expectant management of severe preeclampsia at 28-32 weeks, and a comparison of methyldopa versus labetalol versus no treatment in women with mild chronic hypertension during pregnancy.

Dr. Sibai was previously actively involved in the NICHD protocol, "Collaborative Study on the Effect of Antenatal Dexamethasone Administration on the Prevention of Respiratory Distress Syndrome" (1978-83). Dr. Sibai was the Principal Investigator of one of 7 centers selected by the initial NICHD to form the Matemal-Fetal Medicine Network. During that time, Dr. Sibai was Chairman of the subcommittee for the "Low Dose Aspirin as a Preventative of Preeclampsia" protocol. Results from this trial were presented at several national meetings and led to several publications (the main manuscript being published in the New England Journal *of Medicine).* In addition, Dr. Sibai served as a member of the subcommittee that reviewed the design and completion of the NICHD network "Postterm Pregnancy" protocol, and the subcommittees for the "Preterm Labor" and "PROM"

% = Percentage of Effort

protocols. (See list of MFMU related publications in Appendix C) He has experience in the design and conduct of clinical trials as exemplified by his participation in the "Trial of Calcium Supplementation for the prevention of Preeclampsia and Preterm Births".

As Principal Investigator from Tennessee from 1995-2000 Dr. Sibai participated on the Ad Hoc Committee on Preterm Studies, the Biological Fluids Bank Protocol subcommittee, the Progesterone subcommittee, the Pre-eclampsia Prediction subcommittee, the Capitation committee, and is chairperson for the Concurrent Research. He will devote % of his time to this proposal.

Dr. Joseph Spinnato, Professsor and Vice-Director, Department of Ob/Gyn: Joseph A. Spinnato II, M.D., is Professor and Vice Chair of the Department of Ob/Gyn at the UCMC College of Medicine. Prior to this relatively recent appointment, Dr. Spinnato was Professor and Director of the Division of Maternal Fetal Medicine at the University of Louisville School of Medicine where from 1990 to 1999 he served as Director of the Fellowship Program in Maternal Fetal Medicine. Dr. Spinnato is an active investigator with considerable experience in clinical trials and will be submitting concept proposals to be considered by the MFMU Network.

Dr. Helen How, Associate Professor, Department of Ob/Gyn: Dr. How is currently an Assistant Professor in the Division of M-FM, Department of Ob/Gyn at the UCMC College of Medicine. Dr. How completed her residency and a M-FM Fellowship at the University of Louisville, Kentucky. She is board certified in M-FM and has been extensively involved with clinical perinatal research. Her research interests include preterm labor, preterm PROM and diabetes in pregnancy. Dr. How spends % of her time in research.

Dr. Oormila Kovilam, Assistant Professor, Department of Ob/Gyn: Dr. Kovilam is assistant professor in the Division of M-FM who joined the division following her fellowhip in M-FM at the University of Cincinnati in 1997. Dr. Kovilam completed her residency training at Providence Hospital and Georgetown University in Washington, DC. Dr. Kovilam is active in the MFMU Network.

Dr. Leslie Myatt, Professor, Department of Ob/Gyn: Dr. Myatt is Professor of Ob/Gyn and Pediatrics and Adjunct Professor of Molecular and Cellular Physiology. Dr. Myatt is known nationally and internationally and holds a strong track record of extramural funding both in England and the USA. He has over 130 publications. Dr. Myatt's current research interests include elucidation of mechanisms controlling human fetal-placental blood flow and the study of the signal transduction mechanisms which regulate eicosanoid synthesis and action in fetal membranes and myometrium at the time of parturition. Also, he is currently involved in clinical research projects involving bacterial infection and preterm labor, nitric oxide expression and action in preeclampsia and myometrial sensitivity in preterm labor. Dr. Myatt is actively involved in teaching and mentorship and is the program director for the NIH funded Women's Reproductive Health Research Scholar's program in the Department of Ob/Gyn. He was recently appointed as the Director of the Physician Scientist Training Program (MD/Ph.D) for the College of Medicine. He has supervised six graduate students, eight postdoctoral fellows, eleven M-FM fellows, two neonatology fellows, and four resident research projects. He is mentor to two M-FM research fellows. Dr. Myatt will continue to be available for MFMU network protocol development and projects.Indeed he is the Principal Investigator on the MFMU Preeclampsia Prediction Study which will begin sometime in the current grant period. Dr. Myatt received his B.Sc. and Ph.D. in Biochemistry from the University of London and has devoted his career to perinatal research. He has held positions at Charing Cross Hospital Medical School, University of London and the Institute of Ob/Gyn, Royal Postgraduate Medical School, University of London, and has been at the UCMC for the past thirteen years. He is a past president of the Perinatal Research Society and is currently editor of the journal Placenta. Dr. Myatt devotes % of his time to research.

Dr. Kenneth Clark, Professor, Department of Ob/Gyn: Dr. Clark has been actively involved in perinatal research since 1971. His research has concentrated on the humoral factors regulating uterine and more recently, umbilical blood flow. His studies also include the evaluation of the relationship between uteroplacental blood flow and intrauterine growth retardation. His model of reduced uterine blood flow provides a novel approach to the study of intrauterine growth restriction. Recent interests include the role of placental growth factors (IGF-I and II) in regulating fetal growth and the role of endothelin in regulating systemic arterial pressure, uteroplacental blood flow, and proteinuria. Dr. Clark received his undergraduate degree from Purdue University and completed his doctoral study in cardiovascular pharmacology at the University of Iowa in 1975. He is currently Professor of Ob/Gyn and Pediatrics and Associate Professor of

% = Percentage of Effort

Molecular and Cellular Physiology at UCMC. Dr. Clark is Director of The Large Animal Perinatal Research Laboratory in the Department of Ob/Gyn. In 1993 he received a five year Heart and Lung grant to study the estrogenic regulation of coronary circulation. [%] percent of Dr. Clark's time is allocated to research.

IV. AVAILABLE POPULATION OF CLINICAL RESEARCH SUBJECTS

The population available for clinical research in our institution is optimal in that the same group of neonatologists oversees all inborn NICU's in the region: GSH, University (including approximately 300 maternal transports per year) and the outborn NICU at CHMC, a regional tertiary NICU, including all regional pediatric surgery and ECMO, caring for outborn patients coming from primary and secondary care nurseries from southern Ohio, northern Kentucky and southeastern Indiana. We will first describe the available population of clinical research subjects reflected by NIH MFMU actively, followed by (A) the University Hospital NICU, (B) the Good Samaritan NICU and inborn unit, and (C) the Children's Hospital NICU population.

Obstetrical Population Profile

Annual delivery rates at the University Hospital, Inc.(UHI), the Christ Hospital (TCH) and Good Samaritan Hospital (GSH) have remained relatively constant in recent years as shown in Table 3 for the years 1997-1999. Approximately 80% of the obstetric population at UHI is derived from indigent patients seen in the resident staff clinics with a 50:50 white to black ratio. The TCH and GSH obstetric populations consist mainly of private patients of whom 80% are white. Other minority groups such as Hispanics, Asians, and Native Americans represent only a small fraction in our region. Additionally, 25% of women receiving care at UHI smoke during pregnancy. Of these, approximately 10% smoke 1-5 cigarettes per day, 70% smoke 10-20 cigarettes per day, and 20% smoke more than 20 cigarettes per day.

POPULATION PROFILE

	1997			1998			1999		
	UC	GSH	TCH	UC	GSH	TCH	UC	GSH	TCH
Total deliveries (n)	2085	5086	3426	2301	4766	3468	2230	4607	3581
Multiple gestation (n)	44		69	69		66	67		72
Total infants	2134	5253	3495	2384	4760	3536	2306	4814	3653
Live births (n)	2111	5211	3477	2344	4720	3514	2278	4777	3624
Clinic patient	1211			1252			1784	913	
Race-white	935	4330	2741	982	3840	2945	984	3908	3018

Sources of Patients

Patients delivering at UHI receive their prenatal care at the Perinatal Treatment Center, Ambulatory Obstetric Clinics, City Health Department and Community Clinics and from the faculty private practice. The UHI and Health Department and Community Clinics patients are followed by MFM faculty, fellows, and resident staff and private patients by the respective full-time faculty of the Department of Ob/Gyn including members of the M-FM and General Ob/Gyn Divisions. The faculty of the M-FM Division have a large high-risk referral population under their care. Referrals of high-risk patients from community physicians presently account for approximately 10% of the obstetrical population. These referrals commonly made in mid or late pregnancy, frequently take place because of premature labor or preterm premature rupture of membranes and/or because of another acute obstetrical or medical problem such as diabetes, hypertension, and multifetal gestation.

The obstetrical patients at TCH are cared for by the private physicians who comprise the TCH Ob/Gyn staff and who have appropriate admitting privileges. Joseph Spinnato, M.D., Vice- Director of the University of Cincinnati Department of Obstetrics and Gynecology, is based at the TCH Perinatal Center and is available for consultation for high risk patients. He is also responsible for all Level II ultrasounds that are performed in that center. Patients <32 weeks gestation who are at risk for delivery are referred to UHI for management and delivery.

The GSH obstetrical patients are derived from two sources: from the resident staff clinics and from the private physicians who comprise the GSH Ob/Gyn staff and who have appropriate admitting privileges. In addition, as a result of the four M-FM subspecialists based at GSH, there are a significant number of high risk referrals similar to the referrals to UHI. All obstetric ultrasounds and ultrasound guided procedures are performed in the GSH Seton Center, the Perinatal Center for GSH.

Prematurity Rate

The prematurity rates at UHI, TCH, and GSH have remained fairly constant the last 3 years as shown in Table 4 and the contribution of prematurity to the overall perinatal mortality is shown table 5. The perinatal mortality rates are significantly influenced by infants whose birth weights are less than 1,000 grams. These infants account for less than 4% of our delivery rate yet they account for over 70% of our perinatal loss rate. The 88% of infants born with birth weights of 2,500 grams or more account for only 8% of the perinatal mortality rate. The prematurity and neonatal mortality rate at TCH is lower than at UHI and GSH both of which are tertiary care units with NICUs.

PREMATURITY RATE

	1997			1998			1999		
	UC	GSH	TCH	UC	GSH	TCH	UC	GSH	TCH
Live births	2111	5211	3460	2344	4720	3514	2278	4777	3624
< 1000 gm	55	119	5	81	86	6	78	108	5
1000 - 1499 gm	56	85	7	73	121	10	71	104	7
1500 - 1999 gm	83	140	32	92	126	33	119	148	39
2000 - 2499 gm	191	260	116	219	248	140	214	250	162
≥ 2500 gm	1726	4607	3300	1879	4139	3325	1794	4167	3411

NEONATAL MORTALITY RATE (by birth weight)

	1997			1998			1999		
	UC	GSH	TCH	UC	GSH	TCH	UC	GSH	TCH
Live births (n)	2111	5211	3460	2344	4720	3514	2278	4777	3624
Neonatal deaths	26	42	6	39	42	10	26	58	13
< 1000 gms	19	38	5	32	29	8	20	43	11
1001 - 1500 gms	4	1	0	2	3	0	1	6	1
1501 - 2000 gms	2	1	0	1	3	0	2	2	0
2001 - 2500 gms	1	1	1	1	2	1	0	2	0
≥ 2500 gms	0	1	0	3	5	1	1	5	1

Medical Complications of Pregnancy

The rate of medical complications of pregnancy at UHI is quite high comprising 17% of our total deliveries. Table 6 lists the UHI and TCH complication rates by category: cardiac disease, diabetes, chronic hypertension, pregnancy-induced hypertension and cocaine abuse.

PREGNANCY COMPLICATIONS (Prematurity Excluded)

Complication	1997		1998		1999	
	UC	TCH	UC	TCH	UC	TCH
Cardiac Disease	27	0	29	1	29	0
Diabetes (B-RT)	47	7	41	9	48	11
Chronic hypertension	82	61	49	19	52	43
Pregnancy-induced hypertension	218	105	201	109	203	112
Cocaine abuse	103	0	73	0	102	0

Mode of Delivery

Our institutions' rate of cesarean section deliveries has remained relatively constant with an overall cesarean section rate of 20-21%. Cephalopelvic disproportion, failure to progress, malpresentation and fetal distress comprise the majority of listed indications for primary cesarean sections. Table 10 lists modes of delivery at our institutions.

MODE OF DELIVERY

	1997			1998			1999		
	UC	GSH	TCH	UC	GSH	TCH	UC	GSH	TCH
Total deliveries (n)	2085	5086	3426	2301	4766	3468	2230	4607	3581
Vaginal deliveries (n)	1669	4199	2722	1869	3854	2808	1770	3728	2764
Total cesarean sections (%)	419 (20)	887 (17)	704 (21)	432 (19)	912 (24)	660 (20)	460 (21)	879 (20)	817 (23)
Repeat C-S (%)	141 (34)	258 (29)	328 (47)	160 (37)	281 (31)	275 (42)	126 (27)	301 (34)	327 (40)

A. NIH Maternal-Fetal Medicine (MFM) Units Network: (NIH Grant #HD 27905-05)

The Division of Maternal-Fetal Medicine is one of 4 divisions of the Department of Obstetrics and Gynecology, chaired by Dr. Baha M. Sibai. This department ranks among the top 10 nationally in NIH grant funding. There are 24 full-time faculty, 10 in the Division of Maternal-Fetal Medicine with an active, accredited, Maternal-Fetal Medicine Fellowship training program. There are currently 4 Maternal-Fetal Medicine fellows.

Tariq Siddiqi, M.D. is the Principal Investigator and the primary active collaborator in protocol development for the MFMU. Dr. Siddiqi is a board certified obstetrician/gynecologist, as well as a board certified maternal-fetal medicine specialist. His residency in obstetrics and gynecology was at St Agnes Hospital in Baltimore, Maryland. His fellowship in Maternal-Fetal Medicine was at the University of Cincinnati from 1981-1983. While serving as Director of the Ultrasound Division and Director of Maternal-Fetal Medicine, Dr. Siddiqi has been extensively involved with clinical research. He devotes approximately half of his time to research (95% of which is clinical).

UCMC MFM Units Clinical Trials:

As one of the 13 current clinical centers in the NICHD MFMU network, the UCMC investigator team has proven experience in screening, recruitment, and implementation of multicenter studies. The UCMC investigator team has participated in every network protocol initiated to date. Patient recruitment for the network studies occurs in multiple sites; the UCMC Perinatal Center, the University Hospital Obstetric Clinic, seven outlying City of Cincinnati Health Department Clinics staffed by physicians from the MFM Division at the University, private practices of faculty in the department of Ob/Gyn, and since August 1994 the Christ Hospital. Routine coverage by maternal-fetal faculty at the high-risk and low risk clinics allows for easy identification of patients for recruitment. A faculty member of the MFM staff is on site at The Christ Hospital. In addition, UC residents do 24 hour coverage there which makes patient identification of study patients much easier.

On-going Trials:

1. **Randomized Clinical Trial of the Beneficial Effects of Magnesium Sulfate**: Enrollment into this study began in January, 1998. The purpose of this trial is to determine if magnesium sulfate, administered to the mother prior to delivery, will reduce the infant's risk of developing cerebral palsy as a result of preterm birth. Fifty-one patients have been enrolled into this study out of 260 patients screened for the study.

2. **Randomized Trial of 17 Alpha-hydroxy Progesterone Caproate for the Prevention of Preterm Birth in High Risk Women**: This randomized clinical trial was designed to determine whether weekly injections of progesterone will reduce the risk of preterm delivery in women who have a history of preterm deliveries. Sixteen patients had been randomized to the protocol in the first year. However, the study was suspended by the MFMU network on March 15, 1999 because the 17 alpha-hydroxy progesterone caproate was

recalled by the manufacturer. Randomization into the study restarted in October, 1999 and there have been 5 patients enrolled since that time.

3. **An Observational Study of Cesarean Section and Vaginal Birth After Cesarean Section**: The purpose of this study is to determine the cesarean rates, indications for operative intervention, intrapartum patient management and outcome by payer and provider status. At our center, 1966 charts have been reviewed, including 1603 cesarean sections. In addition, 363 charts of women who had vaginal births after cesarean section (VBAC) were reviewed.

4. **Prospective Randomized Placebo-Controlled Trial to Determine Safety and Efficacy of Antenatal Corticosteroid Regimens**: The question to be studied in this protocol is in patients less than 32° weeks gestation who are at risk for preterm delivery and who are still pregnant more than seven days after an initial course of corticosteriods, is weekly readministration of corticosteroids until 34 weeks more efficacious in preventing neonatal morbidity and mortality than a single course of corticosteroids? Since April 2, 2000, 6 patients have been screened and one randomized. This study includes a 3 year follow up for the infants which will be completed at the Children's Hospital Medical Center follow-up clinic.

5. **A Prospective Observation Study Evaluating Obstetric Outcomes in Women with the Factor V Leiden Mutation**: There have been 43 patients randomized. The purpose of this study is to determine how many pregnant women who develop pregnancy related thromboembolism are carrying the factor V Leiden mutation in their blood.

6. **Randomized Clinical Trial of Oral Terbutaline for Preterm Labor Suppression After Acute Tocolysis:** This trial was designed to evaluate the effectiveness of oral Terbutaline in preventing the recurrence of preterm labor in women who had been treated for an acute episode of preterm labor. Only 4 patients were randomized to the clinical trial and 1 patient was randomized to the observational study. There were a total of 49 women randomized in the entire network so the study was discontinued by the MFMU Network in July of 1999.

7. **Randomized Trial of Metronidazole Plus Erythromycin To Prevent Preterm Birth In Women With Elevated Cervical/Vaginal Oncofetal Fibronectin**: This randomized trial was proposed to determine if antimicrobial therapy will reduce preterm birth in women with elevated oncofetal fibronectin. 809 women have been screened and 9 patients have been randomized. The recruitment in our center is in accordance with the analysis performed by the Biostatistical Center at the completion of the Preterm Prediction Study projecting that 1-2% of women in our center would test positive for fetal fibronectin.

Completed Trials:

1. **Assessment of Home Uterine Activity Monitoring For the Prediction of Preterm Labor/Delivery**: The purpose of this trial was to examine the frequency and patterns of uterine contractions in women delivering prematurity as compared to women delivering at term. 65 patients were randomized at UCMC including 13 twin mothers, 41 patients with previous preterm deliveries or second trimester bleeding, and 11 low risk mothers as controls.

2. **An Observational Cohort Study to Evaluate the Effects of Asthma and Treatment Regimens on Perinatal Outcome**: The primary objective of this study was to determine whether the frequency of preterm delivery at less than 32 weeks gestation is higher among patients with moderate and severe asthma than among non-asthmatic controls. UCMC enrolled 98 moderate/severe asthma patients, 104 mild asthma, and 112 control patients for this study 12% of network recruitment. Of the 314 recruited patients only 12 patients (3.5%) were lost to follow-up.

3. **A Randomized Clinical Trial of Theophylline Versus Inhaled Beclomethasone in the Treatment of Moderate Asthma During Pregnancy**: This was a collaborative study involving the National Heart Lung Blood Institute and the National institute of Child Health and Development (NHLB/NICHD) to establish a multicenter, prospective, double-blind, and randomized clinical trial of theophylline versus a treatment of inhaled beclomethasome in moderate asthma during pregnancy. UCMC randomized 12% of all recruited patients which ranked us 4th in patient recruitment.

4. **Effect of Metronidazole on Pregnancy Outcome in Women Infected with Trichomonas Vaginalis or Bacterial Vaginosis**: This study was initiated to determine if metronidazole therapy would reduce the risk of preterm delivery in women infected with asymptomatic bacterial vaginosis or asymptomatic *T.*

Vaginalis. Screening for bacterial vaginosis ended January, 1998 and screening for trichomonas vaginalis officially ended in October, 1998. There were 2038 subjects screened at our center and 177 of those were randomized to either antibiotic therapy/ placebo. U.C. surpassed the target set by the Biostatistical Center for screening and randomization into this trial.

The UCMC Pharmacy prepared the medication and placebos for this trial for all participating MFMU centers.

5. **Registry of Maternal Varicella-Zoster Virus Infections in Pregnancy**: This study began in June of 1993 and recruitment ended in March of 1998. The purpose of this study was to determine the frequency, nature, and severity of congenital defects in women with clinical evidence of varicella infection during pregnancy. 16 women were randomized into this study at our center.

6. **Placental Pathology**: In 1992 Dr. Robert Bendon, UCMC pathologist, submitted an ancillary pathology study to the preterm PROM protocol. The study was designed to test the hypotheses: (1) that antibiotic therapy has a biologic effect on the membranes in cases of preterm premature rupture of membranes; (2) that there are two distinct mechanisms of premature rupture of membranes: (a) rupture due to membrane necrosis or retromembrane hemorrhage and (b) rupture due to pathology at the cervical os; (3) to validate a standard terminology for the wide range of histologic observations of placental membranes; and (4) to find clusters of associated microscopic membrane features that may have clinical significance. The UCMC and Dr. Ana Faye Peterson at the University of Alabama (UAB) collected 240 non-PROM control placentas to determine whether gestational age at labor, or duration of ruptured membranes during labor, independently affect histologic manifestation of the membranes. The results of this ancillary study have been published in Pediatric Developmental Pathology 2:552-558, 1999.

University of Cincinnati Subjects Enrolled in MFMU Studies (4/1/96 - 5/10/00)

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Asthma Obs	0	0	96	0	69	2	167
Asthma Trial	0	0	22	0	7	0	29
BV/TV Trials	0	0	83	1	34	0	118
FFN Cohort	0	0	346	6	239	63	654
Cervical U/S	0	0	11	0	1	0	12
BEAM Trial	0	0	20	0	30	1	51
Progest Trial	0	0	10	0	11	0	21
Terb Trial	0	0	2	0	2	0	4
Terb Obs	0	0	2	0	2	0	4
C/S Registry	1	25	555	12	1474	33	2100
Steroids	0	0	0	0	1	0	1
Factor V	0	0	22	0	4	0	26
TOTAL	1	25	1175	19	1877	99	3196

B. Women's Health Initiative - Clinical Center for the Clinical Trial and Observational Study (N01-WH-4-2126): The Women's Health Initiative (WHI) was initiated by the NIH to address longstanding and fundamental gaps in the knowledge about women's health by investigating a wide range of illnesses in women, specifically chronic diseases affecting mature patients. There were only 4 Ob/Gyn Departments

selected to participate in the study among the 40 WHI clinical centers in the country. The Department of ObGyn at the UCMC with James Liu, M.D., as principal investigator, is one of these clinical centers. Our center currently follows 1400 subjects in the Clinical Trial and over 2000 participants into the Observational Study.

C. Gynecology Oncology Group Clinical Research Grant (National Cancer Institute): The Gynecologic Oncology Group (GOG) is a cooperative group of investigators founded in 1970 for the purpose of conducting clinical research in the field of gynecologic cancer. It is the only known group which deals exclusively with clinical research in gynecologic cancer. In 1989 the division of Gynecologic Oncology at UCMC became a full member in the GOG with Nader Husseinzadeh, M.D., as principal investigator.

D. The University Hospital NICU serves a high-risk, indigent, African-American and Appalachian population in addition to maternal transports of high-risk pregnant women from all over the region. The average daily census is approximately 30 with 6-7 ventilator babies. There are 61 full-time and 20 part-time RNs; 15 full-time and 9 part-time RTs. There are 3 Neonatal Pharmacists, one Neonatal Nutritionist and one Social Worker. There is a long established Neonatal Database linked to the hospital's clinical and decision support databases. Payors are distributed 60% Medicaid, 10% self-pay and 30% commercial insurance.

E. Good Samaritan Hospital Obstetrics/NICU: The Good Samaritan Hospital (GSH) has the largest obstetrical unit in Cincinnati. The full-service NICU is staffed by Division of Neonatology faculty, Neonatal Nurse Practitioners, University of Cincinnati Pediatric Residents and Division of Neonatology fellow. Pediatric Surgeons from CHMC perform PDA ligations, central line placements and other selected procedures at GSH. Major surgical cases including cardiothoracic surgery, neurosurgery and ECMO are transported by our Transport Team to CHMC. Full diagnostic radiology services including color Doppler ultrasound, echocardiography staffed by University Pediatric cardiologists, CT and MRI are available in house. Both conventional and high frequency oscillatory ventilation are used. A Neonatal Pharmacy is available including total parenteral nutrition services. There is a computerized Perinatal Database that includes all Good Samaritan Hospital Obstetrical patients and newborns. Neonatologists who work in the GSH NICU are members of the Division of Neonatology who participate in medical student/resident teaching, clinical research and Divisional committees/meetings. Good Samaritan Hospital became a NICHD Neonatal Research Network hospital September 1, 1995. Since that time, **Good Samaritan neonates have participated in the following Network studies: 401-1500 gm Registry (GDB), Follow-up, Vitamin A, SAVE, Glutamine and Surfactant/CPAP.**

The Good Samaritan Hospital NICU averages 650-700 neonatal admissions per year. This NICU is a brand new state-of-the-art NICU opened in 2000. 99% of admissions are inborn with a large high-risk, referral obstetrical population served by 3 full-time, academically oriented, board certified Maternal-Fetal Medicine subspecialists. There are 46 beds with an average daily census 35 with an average daily ventilator census of 5. There are 42 full-time and 42 part-time RNs and 7 full-time and 9 part-time RTs. There is one Neonatal Pharmacist, one part-time Neonatal Nutritionist and one Social Worker. Good Samaritan participates in the Vermont Oxford database as well as the NICHD Neonatal Network. Payors are distributed 72% Medicaid or managed care, 25% commercial indemnity and 3% self-pay.

F. The Regional Center for Newborn Intensive Care at Children's Hospital Medical Center averages 600-650 neonatal admissions per year. This NICU is the only regional center for quaternary care including all Pediatric Subspecialties, Pediatric Surgery and surgical subspecialties, Cardiothoracic Surgery and Cardiac Transplant Service, full-service Pediatric Radiology Services (including ultrasound, MR, CT), ECMO, HFOV and inhaled nitric oxide. There are 56 beds with an average daily census of 32 and an average daily ventilator census of 10. There are 6 full-time and 85 part-time RNs, 11 full-time and 5 part-time RTs and 3 PRNs. There are 2 Neonatal Pharmacists, 4 Neonatal Nutritionists and 2 Social Workers. Payors are distributed 45% Medicaid, 35% managed care, 17% commercial indemnity and 3% self-pay.

G. Referral and Transport Patterns

A regionalized perinatal health care system began in Cincinnati in 1977 and is one of the few programs surviving essentially intact in the U.S. A systems approach is used in which components in a geographic area are defined and coordinated. The system emphasizes communication, education, consultation and professional

competence to maximize the utilization of perinatal clinical services according to patient needs. Neonatologists from the Division of Neonatology are currently available to see patients in six community Level II hospitals, St. Elizabeth, Christ, Bethesda North, Mercy Anderson, Franciscan Mount Airy, and Mercy Fairfield Hospitals, in addition to the 3 university affiliated NICU's. This means that the Division of Neonatology is involved in the care of 25,000 of the 30,000 annual deliveries in our region. This activity ensures continuing maternal transports to University Hospital/Good Samaritan Hospital and neonatal transfers to Children's Hospital Medical Center. Through this regionalized system, the Perinatal Outreach Program of the Division seeks to improve perinatal care and thereby reduce associated mortality and morbidity in our Region. Our region, as defined by the Federal Government Health System Geographic Localization, is called Region I of the Central Ohio River Valley Association (CORVA). There are 18 regional obstetric units in Region I. Region I consists of eight Ohio counties which are Hamilton, Adams, Brown, Highland, Butler, Warren, Clermont and Clinton. In addition, CORVA officially includes the three northern Kentucky counties of Boone, Kenton, and Campbell, and unofficially serves as a perinatal resource for four counties of southeastern Indiana (an area tied together by economic, geographic and service considerations).

The Children's **Neonatal Transport Team** transports via ambulance, helicopter, prop plane and Lear jet. The Team primarily services hospitals in southwestern Ohio, northern Kentucky and eastern Indiana. Due to the CHMC Extracorporeal Membrane Oxygenation (ECMO) program, the Team transports from many states in the Eastern United States, i.e. Michigan, Tennessee, Florida, New York. CHMC also goes outside the immediate region for the transport of patients requiring otolaryngology consults and cardiac consults. The Team transports in for highly specialized outpatient tests and returns the neonate after the test. Our dedicated, full-time Team consist of 9 nurses, 9 respiratory therapists, an administrative director, and a neonatologist as co-medical director. The Team provides services, 24 hours a day 365 days a year.

Referrals are made by physicians and called in by physicians and/or nurses per telephone. Information is gathered on the status of the neonate by physician, nurse (RN) or respiratory therapist (RT). Stabilization information is relayed as needed. The Team is RN/RT or RN/RT/MD with the composition of the Team depending on the level of care that the neonate requires. The MD component is a neonatologist or neonatal fellow. The Team leaves no later than 20 minutes after the referral call is initiated. The Team attends deliveries, resuscitates, stabilizes and cares for the neonate as needed.

When a neonate no longer requires the specialized services of CHMC's Regional Center for Newborn Intensive Care, the neonate is reverse transported. Each case is handled individually and is dependent upon the referral hospital's availability and ability to care for the neonate as well as that of a physician willing to assume responsibility for the neonate's care.

V. FACILITIES AND CLINICAL CAPABILITIES

A. Clinical Care

Data regarding outcomes are closely monitored by a systematic quality improvement program. All deaths are formally reviewed by the attending physician and fellow and a retrospective analysis performed with critiques and written recommendations. In addition, selected patients are formally reviewed by an independent neonatologist at every monthly perinatal mortality meeting, open to all perinatal/neonatal faculty, fellows and staff. Clinical services for the Division of Neonatology are divided into three areas: 1) NICU's at University, GSH and CHMC; 2) a High-Risk Follow-up Program located at the Children's Hospital Medical Center; and 3) an outreach program directed towards patient care, consultation and education in the community; all community hospitals have a neonatologist and maternal/fetal medicine consultant assigned. One attending physician is assigned to the NICU services at each of the three NICU's (UH, GSH and CHMC). Each attending physician, along with a fellow, nurse practitioners and 3 to 5 residents, organizes, supervises and manages all patients located in each of the NICU's. The attending physicians are assigned on a biweekly or monthly basis and are responsible for all patient care related activities for that month. Each patient is seen on a daily basis by the attending physician. The attending physicians are intimately involved with the daily aspects of care and are approached for all protocols to be implemented in the nurseries. Attending physicians are notified about all new admissions. Attending physicians often attend high risk deliveries. A neonatology fellow or attending is required to be present at all deliveries below 32 weeks gestation, infants with congenital

anomalies, preterm multiple births, etc. Attending physicians and fellows of the Division meet on a monthly basis to review the care and issues concerning patient care in the NICU's. This meeting is held jointly with the nursing and respiratory therapy departments. There is a neonatology fellow in-house 24 hours a day to cover all immediate and urgent needs of patients. This ensures that all new patients who are admitted and might be eligible for studies are appropriately identified in order to be recruited and enrolled.

B. NICU Treatment Philosophy

Attending physicians meet twice monthly to discuss more detailed issues related to organization of services and care of patients. At these meetings, new breakthroughs are discussed, the scientific literature reviewed and, if appropriate, recommendations made regarding implementation of these approaches. Problems identified by clinical faculty and fellows as areas of confusion are reviewed or assigned to individual faculty or fellows for development of protocols. Such protocols are discussed and approved by the division at these clinical faculty meetings.

All clinical research protocols submitted to the Institutional Review Board (IRB) that concern newborns are first reviewed by the Division of Neonatology and approval or disapproval recommended upon the strength of the protocol, its scientific merit, and its adherence to ethical principles. New ideas for management are subjected to review by all members of the Division of Neonatology through weekly Neonatology Grand Rounds and Clinical Division Faculty Meetings and when appropriate, protocols are developed to standardize patient care. Faculty members of the Division of Neonatology are deeply committed to clinical research and are very supportive of any research protocols that are generated in or outside the division. This has allowed for extensive collaboration in research on newborn infants with members of other divisions and departments as well.

C. NICU Facilities and Physical Plant

The 6.5 million dollar ultramodern NICU at University Hospital is a spacious 23,000 square feet (17 foot ceiling) facility and accommodates 50 patients. This NICU provides state-of-the-art technology and facilities including bedside computer terminals with individual patient displays as well as ward-wide Alcyon computer and blood gas graphic displays. Located in the NICU is a dedicated satellite neonatal chemistry laboratory, a satellite neonatal pharmacy, numerous breast feeding rooms, and dedicated "home style" family rest and living quarters and lounges and a sibling play area. The NICU is located on the third level of the new critical care tower adjacent to the delivery and post partum areas and OBSCU.

The Regional Center for Newborn Intensive Care (RCNIC) at CHMC which opened in December, 1993 is housed in the new CHMC Critical Care Tower with the emergency room, radiology, operating rooms, pediatric intensive care and bone marrow transplant units. This unit includes a total of 25,000 square feet with approximately 150 square feet per bed space accommodating up to 56 patients. This nursery serves outborn surgical, ECMO and medical neonatal patients. The RCNIC is designed to allow for individual lighting, noise control and traffic control. Parents have access to five breast feeding/consultation rooms, an overnight room and a spacious waiting area. The patient to caregiver ratio averages 2:1 but is continuously altered to meet the needs of the patients. Numerous computer terminals allow linkages with the laboratory, pharmacy and Alcyon system. An on-site blood gas and micro-chemistry laboratory staffed 24 hours a day allows for prompt results needed for the critically ill neonate. Parent and support spaces are provided allowing for efficient administration and care.

Good Samaritan hospital provides perinatal services for approximately 4800 deliveries a year. Four, board-certified perinatologists provide consultation and/or management (outpatient and inpatient) of high-risk obstetrical patients. The Seton Center located one floor below labor and delivery offers high level ultrasonography and minimally invasive testing. More invasive interventions such as cordocentesis are done within labor and delivery. There is a 21 bed high risk antepartum unit which typically runs at or near capacity and is in the process of renovation and expansion. There are 4 additional high risk beds located within labor and delivery. Admissions to the inpatient high risk service include maternal transports from other community hospitals which number approximately 180 per year. There are 12 labor and delivery suites and 41 single postpartum rooms, which can be converted to double occupancy as required.

There is a newly renovated 46 bed NICU located next to labor and delivery with 650-700 annual admissions. Since opening April 2000, average daily census has been 40. The NICU is staffed by 7 University

of Cincinnati neonatologists, 42 full and 42 part-time NICU nurses, 9 full and 7 part-time respiratory therapists and 1 part-time nutritionist. On-site support in subspecialty areas such as ophthalmology, pediatric cardiology (including echocardiography) and pediatric surgery is provided through the Children's Hospital Medical Center.

D. Prenatal Care Clinical Facilities: Regional Perinatal Center

In September 1990, the University Hospital's Regional Perinatal Center relocated to the third floor of the ambulatory building which is adjacent to University Hospital. There are 13,000 sq. feet in the new Perinatal Center which includes 14 examination rooms, a large reception and waiting room, consultation rooms, an ultrasound division, an antepartum testing unit, and a fetal echocardiography division. Equipment is available for routine obstetrical care and testing collection and immediate blood glucose analysis, and specialized diagnostic/surveillance/amniocentesis sonography.

E. Pediatric Subspecialists: A full range of University of Cincinnati faculty Pediatric Subspecialists are available to consult and/or care on-site for neonatal patients in any of our three NICU's.

F. Neonatal Respiratory Therapy

Respiratory Therapists in the Regional Center for Newborn Intensive Care (RCNIC) at CHMC work as part of a team known as Neonatal Services. This effort was multidisciplinary by design and three caregiver roles are identified: Care Coordinator (RN and/or RRT), Care Clinician (LPN and/or CRTT), and Clinical Support Technician. All roles work collaboratively providing direct care and family support.

The Respiratory Therapists in the RCNIC offer an expanded scope of respiratory care services including some general nursing care. All of the Respiratory Care Services are performed by a staff of 18 Respiratory Care Practitioners (RCP's) composed of 16 RRT's and two CRTT's. The total FTE complement equals 15.5 and a core number of 3 RCP's per shift has been determined as the ideal standard. The RCP are divided into four work teams located in patient care pods.

Ventilators are maintained by the Respiratory Therapy Department, including Drager, Sechrist # 100 B which is the primary ventilator (n= 26). Eleven Infant Star ventilators are also available. The Sensormedics HFOV 3100 A is the oscillator used with three in house. Five Drager Baby Logs were purchased.

The RCNIC RCP's have participated in the following research studies: The Dexamethasone Study, the STOP-ROP study, the initial Nitric Oxide Study, the Early Nitric Oxide Study and the Surfactant/CPAP study.

Similar on-site Respiratory Therapy services are available at University Hospital and Good Samaritan Hospital.

G. High-Risk Obstetrical Units

Perinatal Special Care Clinic (PSC)

The Perinatal Special Care Clinic (PSC) is a clinic designed to provide care to patients who require intense observation of their medical status as well as the status of the fetus. All patients who require antepartum fetal surveillance would routinely be seen in this clinic.

- **Medical Complications of Pregnancy Clinic (MCPC)**

The Medical Complications of Pregnancy Clinic is a clinic designed to provide care to those patients with specific medical complications requiring the ongoing care of specialists in internal medicine.

- **Adolescent Clinic**

Adolescent obstetrical Services have been provided by University Hospital since July of 1977. Teenagers are followed on a weekly or biweekly basis throughout their pregnancies in this special setting described to better meet their educational, developmental and psychosocial needs. They have the services of a Certified Nurse-Midwife, a Registered Nurse, and a Registered Dietician at each visit. The Clinic is supervised by the Obstetrical chief resident on service and a Maternal-Fetal Medicine staff member.

- **Genetic Amniocentesis Clinic**

The Genetic Amniocentesis Clinic is a clinic designed to provide counseling and appropriate genetic studies for patients desiring genetic evaluation. This clinic is staffed by geneticists and genetic counselors from the University's Genetics program as well as by Maternal-Fetal Medicine faculty. A growing segment of this clinic's activity is the evaluation by ultrasound of fetuses at risk for congenital anomalies. Following documentation of anomalies, management plans are discussed among appropriate experts and implemented. In

1994, 944 amniotic fluid samples were collected.

- **The Perinatal Loss Support Clinic** is a clinic designed to provide support and evaluation of patients with recent pregnancy loss whether early or late. This clinic is staffed by faculty from the Maternal-Fetal Medicine Unit, Social Work staff, the Hospital Chaplain Service and the Patient Relations Service. The members of this clinic staff utilize interview techniques in order to determine and treat problems associated with loss of a fetus or newborn.

Each of these clinics is staffed by one or more of the Maternal-Fetal Medicine faculty. It is expected that our participation in the Cooperative Multicenter Network of MFMUs would involve recruitment of patients in the antepartum period from these clinics as well as from our low risk obstetrical clinics. Routine coverage of the high risk as well as the low-risk clinics by our staff should make identification of appropriate patients for recruitment into various clinical trials very feasible.

University Hospital Obstetrical Services

The obstetrical/delivery unit consists of 10 labor rooms, 4 birthing rooms, 5 delivery suites, a 12-bed recovery unit, and up to 80 beds for antepartum and postpartum care. The labor rooms are equipped with 20 bedside fetal heart rate monitors. The units include a small laboratory equipped for blood gas analysis.

Antenatal Testing Facility: Antenatal fetal heart rate testing is available on a 24-hour basis on the Obstetrical Special Care Unit.

Ultrasonography: The Obstetrical Ultrasound Section of the Division of Maternal-Fetal Medicine is very active in clinical services and research. The program is under the direction of Dr. Tariq A. Siddiqi, Professor and Director of Maternal-Fetal Medicine.

Intrapartum Diagnosis: Laboratory Testing: All standard laboratory techniques are available through the Laboratory Medicine Department under the direction of Dr. W. Vine. Fetal scalp pH analyses are available on a 24-hour basis on the Obstetrical Special Care Unit performed under the direction of Laboratory Medicine personnel. Genetic biochemical analysis of amniotic fluid is accomplished through the Division of Human Genetics under the direction of Drs. Peter Dignan and Shirley Soukup. Pathologic analysis of placental, fetal, and neonatal tissue is carried out under the direct supervision of Dr. Jerzy Stanek, Assistant Professor of Pathology and Laboratory Medicine, University of Cincinnati Medical Center.

H. Support Services

The Division of **Radiology**, headed by Dr. Janet Strife, includes 11 board certified pediatric radiologists and state-of-the-art radiologic facilities and equipment. Several portable and non-portable x-ray and ultrasound Doppler machines are available for studies in the nursery as well as in the x-ray department. Children's, Good Samaritan and University Hospitals each have their own CT scanners and Magnetic Resonance Imaging (with spectroscopy), which are routinely used for the benefit of our neonates.

An important resource for clinical research is our **Imaging Research Center**. Directed by Dr. William Ball, the IRC faculty include clinician scientists, PhD's and post-doctoral students who work collaboratively with other investigators to provide state-of-the-art advanced imaging technology for clinical and basic science research. Funded initially by industry, the Department of Radiology and the Children's Hospital Research Foundation, the IRC expects to be fully externally funded (primarily NIH) for operating expenses within the next 3 years. Currently available technology in this single, core, University of Cincinnati/CHMC facility include magnetic resonance imaging and spectroscopy, high-resolution color Doppler ultrasound, perfusion/diffusion brain imaging, CT, proton spectroscopy, etc. Ongoing studies include in utero spectroscopy, ultrasound tissue characterization in neonatal hypoxic-ischemic encephalopathy, cortical activation MR studies, brain myelinization and high-energy phosphate spectroscopy in brain injury.

Children's Hospital **Clinical Laboratory Services** of Children's Hospital consist of Bacteriology, Virology, Chemistry and Hematology. The Blood Bank is separately operated by the combined University services of Hoxworth Blood Center. Anatomic and Surgical Pathology and Cytology are provided by the Division of Pathology. The main laboratories listed above offer a comprehensive array of diagnostic tests.

There are numerous specialty laboratories within Children's Hospital Medical Center that are operated by Divisions within the Department of Pediatrics. These include the Laboratories of Endocrinology, Nephrology, Respiratory, Enzymology, Special Hematology/Oncology, Gastroenterology, Allergy, Metabolic Disease, the Chromosome Laboratory and Electrophoresis Laboratory. The Clinical Laboratories are accredited by JCAHO.

I. Investigational Drug Services, University of Cincinnati Medical Center and CHMC

One of the highlights of research services/programs at the University of Cincinnati is the availability of one of the nation's largest university-affiliated, academically oriented pharmacy systems. The current NICHD Network has made extensive use of this service for organization and distribution of study drugs (Dexamethasone, Phenobarbital and Vitamin A studies) to the participating Network centers. See letter of support in Appendix I.

J. Modification of Clinical Programs to Accommodate Clinical Research

The Division of Neonatology has a streamlined system for coordination of research protocols in the NICU. This has been particularly important when several protocols are performed on an individual subject. Enrollment of infants for clinical research protocols in the NICU is coordinated by a nurse Clinical Research Coordinator.

Studies in the NICU are classified into 1) nutritional studies; 2) studies involving blood or radiation exposure; 3) studies involving no blood or radiation exposure, but require informed consent; and 4) studies which do not require informed consent. Institutional Review Board approval has been granted for the following combinations of studies in the same subject: 1) any study which does not require informed consent does not exclude the patient from participation in another study; 2) any infant participating in a study that does not require blood or radiation exposure can participate in any of the other studies; 3) in general, an infant can only participate in one nutritional study at a time (approval for combinations of nutritional protocols are separately submitted to the IRB); and 4) patients enrolled in a nutritional study can be enrolled in another study involving blood and radiation exposure only after IRB approval has been obtained for the combination of studies. Any other studies not covered by these guidelines will follow this general approach, with the IRB serving as the final arbiter.

Whenever a patient previously recruited for a study is considered for another study, the Clinical Research Coordinator, who is available 24 hours a day by voice pager, is contacted. If there is no conflict as far as overlapping studies requiring blood sampling and radiation exposure, the attending physician in the nursery is notified by the investigator and a copy of the informed consent, once obtained, is placed in the front of the infant's chart. All cribs of study patients are marked to identify the infant as a study participant. Each study has a unique label that is attached to the crib. Any blood drawn from infants in the NICU for research purposes requires documentation on a special "fluorescent" green sticker in the progress notes, which is completed by the investigator obtaining the blood sample, using standardized IRB approved blood volume limits.

Within the NICU, a notebook containing all copies of all active protocols is maintained. The number of infants who are participating in more than one study are listed in order to monitor whether an infant is being enrolled in conflicting studies. These procedures have worked extremely well and have ensured that multiple blood sampling and excess radiation exposure do not occur in this population of infants.

Definitions for data items in our Divisional Database now incorporate definitions previously established for the NICHD Neonatal Research Network Generic Database.

In July 1995, the Department of Obstetrics installed the Peritronics 9000C Obstetrical Information Monitoring System (OBIMS). This consists of a PC based local area network (LAN). The hardware includes Intel Pentium servers and PC's. Configuration for the system includes a SQL server and three PC's. The software includes Windows 3.1, Windows NT, Microsoft Access Report and adhoc query software, and Peritronics forms and reporting module. The system will be utilized by clinical obstetrical as well as research personnel to capture clinical perinatal information for clinical and research purposes. Pertinent patient information will be entered via form sets which will include the ACOG Antepartum forms, Admission and Assessment forms and the Labor and Delivery forms. Definitions for data items will incorporate definitions already established by the Maternal Fetal Medicine Units of the National Institute of Child Health and Human Development. These electronic forms can be substituted for the present hand written patient charting documents and the data captured on the forms can be utilized for both departmental statistics and research, for example, hypothesis generation, observational studies and for study feasibility and sample size determination.

VI. NICU FOLLOW-UP PROGRAM

The NICU High Risk Infant Follow-up Program at Children's Hospital Medical Center is a multidisciplinary specialty clinic established in 1976 by Dr. Steichen. Through the clinic we provide: 1) specialized post-discharge clinical services for high risk infants; 2) implement center-based longitudinal research protocols with subsequent development of a regional outreach program for post NICU care and tracking of high risk infants; 3) train residents, fellows, and other healthcare personnel, i.e., OT/PT, Sp/L, NNP, PNP, etc.

Through this system interested researchers have access to both organizational set-up (i.e., coordinators, appointment system, long-term tracking of a longitudinal population, help with data collection and maintenance of clinical databases or access to the clinical database of the existing population) as well as the multidisciplinary services available in the clinic, including behavioral and developmental testing, OT/PT, speech & language, nutritionist. Biological specimens for studies can be collected within the clinic system.

Current (n=4) and last 10 year research protocols (n=14) carried out through the High Risk Infant Follow-up Program are listed in Appendix J:

Clinic Population

All infants weighing less than 1000 gm born at the University Hospital and all infants with a birthweight of less than 1000 gm who are admitted to the Children's Hospital NICU are enrolled in the High Risk Follow-up Program. Private pediatricians may also refer infants to the follow-up program for assessment. Currently, the total clinic population of very low birthweight infants who were or are followed through age 3 years is approximately 400+. Infants with BPD are followed through the clinic and receive specialized medical care as long as they receive oxygen in the home. Respiratory monitoring takes place through the clinic until the patient is weaned off oxygen; additionally, after weaning from oxygen, these infants are followed through the clinical care protocol which includes long-term developmental testing. Regardless of gestation or birthweight, infants with difficult nutritional problems are seen in the high risk clinic. Infants with multiple complex medical problems, regardless of gestational age or birthweight, receive specialized services. Infants discharged home on O2 monitors are followed and managed through the High Risk Follow-up clinic.

Clinic Services

The High Risk Follow-up Program collaborates closely with other specialty clinics, especially the Ophthalmology Clinic, Orthopedic, Neurology, Cardiology, and GI Clinics as well as the Cincinnati Center for Developmental Disorders (CCDD). Services provided on-site by the follow-up care team include: Nutrition evaluation and consultation, Occupational/Physical Therapy, Speech/Language and hearing assessment Developmental assessments—done by program psychometrist working in the clinic (see personnel) or through the Children's Hospital Division of Psychology and Psychiatry. Sara Winter, M.D., developmental pediatrician and director of the CP clinic, is a consultant to the clinic. Developmental intervention—including OT/PT, speech and language development, special cerebral palsy education programs and Parent Infant Nurturing Group (PING) through the Cincinnati Center for Developmental Disabilities (CCDD). The clinic collaborates closely with pediatricians and clinic physicians who will provide well child care for these high-risk infants. With the change in health care resulting in the early discharge of high risk infants, the clinic activity has increased significantly as the clinic provides all back up medical services for home nurses and the early discharge program. Early discharges for preterm infants (if needed) are seen in the clinic within one week of discharge to assure a safe transition from the NICU to home.

In summary, the NICU High Risk Infant Follow-up Program is developed with the concept of providing a comprehensive program for long-term longitudinal research projects as well as long-term, multidisciplinary specialized care for high-risk infants. The clinic maintains its own records and has a clinical database maintained on all high-risk infants followed through the clinic through age 2-3 years. An older population of high-risk infants is available for reseachers who would need access to this group as we have started tracking the < 1000 gm birthweight infants for possible long-term follow-up.

Professional Staff

The High Risk Infant Follow-up Clinic meets two times a week (Tuesday and Thursday afternoon) in the Outpatient Services Building of The Children's Hospital. Director of the clinic is Dr. Jean Steichen and Dr. Anna August is Associate Director. Additional staff includes Dr. Beth Haberman, attending neonatologist.

Neonatology fellows provide medical services and receive training in long-term care of the NICU graduate and in the organization and conduct of long-term longitudinal studies. Sara Winter, M.D., Developmental Pediatrician and Director of the Cerebral Palsy Clinic, is a consultant to the clinic. Debbie Highhouse, RN, BSN is the Clinical Nurse Coordinator of the High Risk Clinic and she is supported by staff nurse, Amy Ross, RN, BSN. Two RN's from Children's Hospital NICU assist with the clinics. Other professional personnel who are part of the Infant Follow-up Program are occupational/physical therapists, speech and language therapists, a developmental psychometrist with an extensive background in infants, a neonatal nutritionist, and social workers.

Research Staff

Research nurses and research nurse coordinators as well as research technicians work in the High Risk Infant Follow-up Clinic as needed for specific research protocols carried out through the Infant Follow-up Program. Tari Gratton, M.A., P.A., has been the Infant Follow-Up Coordinator for the Division of Neonatology since 1994. She has previously been Program Coordinator for 2 large Center-Based Grants: The Diabetes and Pregnancy Grant and the Intrauterine Growth Restriction Grant, awarded to the Division of Neonatology. She has implemented longitudinal follow-up studies for several drug companies with greater than 95% compliance from the study population. She has over 20 years' experience working with low-birth weight infants and neurodevelopmental outcome. Currently, as Follow-Up Coordinator, she is a Gold-Standard for the Neonatal Network and responsible for quality of exams and certification for the Bayley Scales of Infant Development II. She is also a certified neuro examiner for the Neonatal Network. As Senior Research Coordinator for the Division of Neonatology, she has successfully completed follow-up on more than 650 infants in longitudinal studies.

VII. RESEARCH NURSE STAFFING

The current Neonatal Research Network has 5 full-time nurses, 1 Data Entry Coordinator: Marcia Mersmann, RN, Clinical Research Coordinator; Staff Research Nurses Cathy Grisby, RN, BSN; Barbara Alexander, RN; Jody Shively, RN; Holly Mincey, RN; and Michele Boshko, BA, Data Entry Coordinator. In total, their experience with the Neonatal network totals seventeen years. There are a total of 20 Research Nurses or Clinical Research Technicians affiliated with the Division of Neonatology and the MFMU. In addition, GCRC nurses are available to participate in neonatal studies including Network studies. **Details of Research Nurse staffing are included in the Appendix G.**

VIII. INTENT TO PARTICIPATE

The Division of Neonatology at the University of Cincinnati enthusiastically supports this renewal application. We are prepared to continue to participate in Network clinical trials, databases and observational studies according to the terms and conditions of this request for proposal. We clearly express our interest to participate in a cooperative manner with other centers, the NICHD, and the Research Triangle Institute. We believe that our institution has a unique combination of resources which greatly enhanced our ability to be an effective and efficient contributor to Network studies. An expanded inborn and NICU population base, an active and supportive GCRC, a large investigative pharmacy which has served as the central study drug distributor for several Network studies, strong MFMU Network participation and leadership in the Network's follow-up studies, all contribute to our unique ability to provide major support of Network clinical studies.

IX. DEPARTMENTAL AND INSTITUTIONAL COMMITMENTS

A. Departmental Commitment

The Department of Pediatrics and the Department of Obstetrics and Gynecology are fully committed to collaborate in this project. We will continue to share resources (human and materials), and allow free access to each others' databases. In addition the four affiliated maternity/neonatal units are committed to collaborative participation. These institutions recognize the importance of an integrated network of neonatology services in order to sustain cost-effective, regionalized perinatal care. All are committed to collaborative clinical research as an essential mechanism for improving perinatal outcomes.

Letters of support from Dr. Sibai, Chairman of Obstetrics and Gynecology, Dr. T.A. Siddiqi, Director of

Maternal-Fetal Medicine at University Hospital and Christ Hospital , Dr. Thomas F. Boat, Chairman of Pediatrics, and Dr. John Hutton, Dean of the UC College of Medicine may be found in Appendix A along with all other letters of support.

B. Departmental Experience

Our division has participated in many multicenter clinical trials over the past 20 years. The considerable number of patients (approximately 1500 neonatal intensive care admissions per year) is an obvious asset in such studies. The following are the examples of non-NICHD Network multicenter studies in which our division played a major role.

1. Cryotherapy study: A multicenter, controlled, randomized trial of cryotherapy for retinopathy of prematurity (ROP) was started in 1986; this trial was funded by the National Eye Institute, the National Institute of Health, and the Department of Health and Human Services. 23 centers involving 63 nurseries participated, recruiting 3862 patients. Our center, with its 2 nurseries contributed 100 infants to the trial, i.e. 2.6% as a center. This study led to the fundamental finding that cryotherapy is efficient in reducing the risk of unfavorable retinal outcome for threshold ROP.

2. Surfactant Studies: Including the Network's surfactant comparison, the Division of Neonatology has participated in three multicenter, randomized clinical trials of surfactant in newborns with respiratory distress syndrome. Three studies were funded by Abbott Laboratories. The first study, conducted between March, 1986, and October, 1986, evaluated a bovine lung extract in inborn infants 750-1750 gr. Drs. Sutherland and Kotagal participated in the study design along with representatives of six other participating centers. By design, 167 patients were enrolled in this study. It was anticipated that each center would enroll 14-15% of the total patients enrolled. In fact, we enrolled 43 patients or 26%. This study included follow-up evaluation of growth, pulmonary function, and neurodevelopmental outcome of enrolled patients at age 6 months. The principal findings of this study were that a single intratracheal dose of surfactant (100 mg/kg of phospholipid) results in decreased inspired oxygen requirement, decreased ventilator pressures and a decreased frequency of pneumothorax. There were no differences in mortality or incidence of chronic lung disease (NEJM 320:959, 1989).

Our second multicenter, randomized masked trial of surfactant was designed to evaluate the effects of a single intratracheal dose (100 mg/kg of phospholipid) given to preterm (750-1750 grams birth weight) outborn infants with RDS. A total of 34 patients were enrolled. Two centers participated in this study. We enrolled 62% of all study patients. This outborn study included follow-up evaluation of growth, pulmonary function and neurodevelopmental outcome at age 6 months. This study demonstrated that a single dose of surfactant given to certain outborn preterm infants with respiratory distress syndrome results in a decreased inspired oxygen requirement and decreased ventilator pressures. There were no differences in mortality or incidence of chronic lung disease.

Our third multicenter, randomized, masked trial of surfactant was designed to evaluate the effects of up to four intratracheal doses during the first 48 hours of life to both inborn and outborn 600-1750 gram infants with RDS. Patient enrollment began in May, 1988, and ended in September, 1989. Five centers participated in this study and a total of 392 patients were enrolled. It was anticipated that each center would enroll approximately 20% of the patients. Our center enrolled 111 or 28% of all patients enrolled.

In the conduct of current studies the Department of Pediatrics and the University of Cincinnati provided support in a number of areas. The GCRC provided laboratory, radiology and monitoring support for the antenatal phenobarbital, STOP-ROP, Dexamethasone, Vitamin A, EPO, NINOs, and Early INO studies. Our Alcyon Perinatal Database was used extensively for identifying patients eligible for various Network studies. Non-Network research nurses (including MFMU) and clinical research technicians worked collaboratively with Network research nurses in conducting Network studies. Faculty, fellows and residents in both Pediatrics and Obstetrics assisted in recruitment for the phenobarbital and dexamethasone trials. NICU staff nurses assisted in managing oxygen therapy in the STOP-ROP trial. The Department provided ample space, equipment and supplies for Network studies. **See also in Section II the extent of our participation in NICHD Neonatal Research Network trials.**

X. ACCEPTANCE OF BUDGETARY MECHANISMS

We believe that the following will help reduce the cost of Network studies conducted in Cincinnati:

A. **Experience of our personnel**: Our large, cooperative, clinical research team is experienced in patient recruitment and conduct of clinical studies. Intensive recruitment, high eligibility to enrollment ratios and our low drop out rate maximize cost-effectiveness; B. Abundant, existing **facilities**: Our laboratory facilities are modern and well equipped, which will minimize any need for the purchase of expensive new equipment. For many measurements, we would be competitive as a center for Network analyses. As an example, in our surfactant study, samples collected in all the centers for measurement of anti-surfactant associated proteins antibodies were processed in our laboratories, as it offered the most sophisticated and least expensive assays; C. Routinely **discounted lab tests for research**: Our clinical laboratories have previously offered their services at a modest cost when they relate to research performed at the University of Cincinnati; D. **Industry participation**: Each time a new drug/treatment is tested, support from industrial producers should be sought. We have a longstanding successful experience of obtaining industry supported grants. Additionally, we have earned the respect of major food and/or drug manufacturers since our goals have always been clearly understood by industry as scientific truth. We believe we could use this experience efficiently within the network.; E. Access to **GCRC support** including laboratory tests, data collection and scatterbed nursing resources; F. Access to support from our **new Pediatric Imaging Research Center.** External funding is now available for studies which include sophisticated or experimental imaging modalities.

We continue to be willing to participate in the NICHD policy of capitation of research costs on a per subject, per protocol basis, in addition to a base budget. This is attested to in the accompanying letter from Dr. Thomas F. Boat, Chair, Department of Pediatrics.

PROPOSED PROTOCOL CONCEPT

Prevention of lung overdistension to reduce the risk of Chronic Lung Disease in infants 24-27 weeks gestational age (GA)

Background and rationale

The putative etiology of Chronic Lung Disease (CLD, formerly known as Bronchopulmonary Dysplasia) in very immature newborns is small airways and alveolar injury occurring in the early perinatal period. Inflammatory injury may occur as a consequence of one or more common perinatal events: (1) a systemic inflammatory process such as may occur when preterm labor is associated with maternal genitourinary infection, (2) free radical injury induced in a high inspired oxygen environment, (3) mechanical disruption of airways integrity by overdistension of the lung or (4) other factors. The adverse effects of mechanical ventilation (MV) on lungs may be related to lung overdistension (volutrauma) rather than airway pressure itself (barotrauma, Dreyfuss 1988, Hernandez 1989). In animals, the use of large tidal volumes is particularly harmful to the developing lung (Dreyfuss and Saumon 1985; Hernandez 1989; Carlton 1990; Peevy 1990).

Using multiple logistic regression analysis, 2 large retrospective studies each concluded that relative hypocapnia during neonatal MV results in an increased risk CLD (odds ratio of 1.45 and 95% CI 1.04, CI 1.5, 12.0; respectively). Kraybill (1989) performed a multicenter analysis in 235 infants 751-1000g admitted to 10 NICUs. Only low paCO2 on days 2 to 4 of life and male gender were independent predictors of CLD. Garland (1995) analyzed data on 188 infants less than 1700 g at birth. Low pC02 before surfactant therapy was associated with CLD adjusting for measures of illness severity. PCO2 >50 mmHg was associated with a lower incidence of CLD. In these 2 retrospective studies it is not clear whether hypercarbia was associated with lower lung volumes.

In a comparision of neonatal centers with a wide unexplained variation in CLD rates, Avery et al suggested that early and frequent use of CPAP as well as avoiding high airway pressures through permissive hypercapnia may be associated with lower risk of CLD. The Network SAVE trial used a 2X2 factorial design to simultaneously evaluate "minimal ventilation" (permissive hypercapnia) and early stress-dose steroids. Although the study was stopped prior to completing enrollment due to an increased incidence of gastrointestinal perforation in infants who received glucocorticoid, there was a trend toward lower CLD or death in infants assigned to permissive hypercapnia suggesting, possibly, that efforts to increase pCO2 by decreasing inspiratory pressure (as recommended in the SAVE trial) may be effective. This trend was observed despite little difference in pCO2 between groups.

Lung injury presumably due to overdistension may occur at any time and from relatively brief periods of overdistension. Among preterm newborns receiving positive pressure ventilation in the delivery room, air leak may be observed shortly after NICU admission. Both use of continuous positive airway pressure (CPAP) and positive pressure mechanical ventilation are associated with increased risk of neonatal air leak. In order to avoid lung injury due to overdistension, one may need to employ a ventilatory strategy that decreases the likelihood of overdistension from birth until positive pressure ventilation is no longer required. We propose to evaluate a strategy to avoid lung overdistension from birth until mechanical ventilation and/or CPAP are no longer required.

Hypothesis: Initiation of CPAP in the delivery room plus use of mechanical ventilation only for severe respiratory failure plus mechanical ventilation strategies, if needed, that minimize tidal volume will reduce the risk of CLD or death from 0.5 to 0.3 in infants 24-27 weeks GA.

Design and methods: This is a randomized, unmasked trial using a prespecified low lung volume strategy with parental consent obtained prior to delivery whenever possible. All infants who meet the specified eligibility criteria are included regardless of illness severity. To account for center-specific management differences and to account for a marked decrease in CLD risk with increasing gestational age, randomization will be stratified by center and by gestational age category (24-25 vs 26-27).

Eligibility criteria: (1) Gestational age by best obstetrical estimate of 24-27 weeks gestational age

inclusive or, in the case of infants of unknown gestation, birth weight 401-1250 grams, (2) parental consent, (3) attending physician consent, (4) no major congenital anomaly, (5) no symptoms of congenital, non-bacterial infection

Intervention: The intervention begins in the delivery room. Participating centers will agree to give an immediate delivery room trial of CPAP 5 cmH2O prior to initiating assisted ventilation in all spontaneously breathing potentially eligible infants, unless the infant is randomized to the "Usual Care Group" prior to birth. For infants randomized after birth, the assigned intervention will begin as soon as possible after randomization.

"Lower Lung Volume Group" (LLV): Spontaneously breathing infants assigned to the LLV group will remain on nasal, nasopharygeal or endotracheal CPAP if fiO2 < 0.7, pCO2 < 70 and pH > 7.2. Mechanical ventilation (MV) will be initiated for severe, persistent apnea. If MV is initiated because CPAP criteria are exceeded or for apnea, a low tidal volume strategy will be used with ventilator rate >50 and end expiratory pressure > 3 cmH20. Tidal volume or inspiratory pressure (if a pressure-controlled ventilator is used) will be selected as the lowest that maintains fiO2 <0.7, pCO2 < 70 and pH > 7.2. The infant will be weaned to CPAP as soon as possible. Extubation guidelines are: pCO2 < 50 or sooner, pH >7.3 or sooner, fiO2 < 0.4 or sooner. At least daily feedback will be given to the clinicians regarding compliance with the lower lung volume strategy.

"Usual Care Group" (UC): Infants assigned to UC will receive care as directed by the attending neonatologist. For infants in whom consent is obtained after birth, the clinical team will maintain CPAP as described above until the consent decision is made.

Primary outcome: Death prior to discharge or CLD. CLD is defined as requiring supplemental oxygen at 36 weeks postmenstrual age to maintain pulse oximetry saturation greater than 0.89.

Secondary outcomes: Neurodevelopmental outcome at 18-22 months postmenstrual age, duration of oxygen, duration of mechanical ventilation

Sample size: The risk of CLD or death in infants 24-27 weeks is approximately 0.5. To reduce the risk to 0.3 (type 1 error = 0.05, power = 0.8) requires 400 infants, 200 infants per group. This risk difference yields a maximum number needed to treat of 5. We have postulated a relatively large effect size. A reduction of risk from 0.5 to 0.4 would require a sample size of 780 (type I error 0.05, power 0.8).

Safety: The risks associated with the proposed intervention include those associated with delays in usual care (surfactant administration and MV if indicated) and possible hypercarbia due to low tidal volume MV. The study intervention does not preclude early intubation for surfactant administration. If early CPAP results in prevention of atalectasis, the need for surfactant and/or MV may be delayed or obviated. Alveolar hypoventilation and resultant hypercapnia and respiratory acidosis may be acceptable if lung overdistension is avoided (Marini 1993; Feihl and Perret 1994). In the proposed study, the maximum allowable pCO2 is 69 torr. Studies in dogs, monkeys, and rats found adequate tolerance to increasing levels of inspired carbon dioxide (Graham 1960; Stinson and Mattson 1970; Xu 1991). Only uncontrolled studies of permissive hypercapnia have been performed in human adults, and these suggest good tolerance and improved survival (Darioli and Perret 1984; Hickling 1994; McIntyre 1994; Bidani 1994). In a single center randomized study, hypercapnia (45-55 mmHg) versus normocapnia (35-45 mmHg) during the first 96 hours of life in neonates 601-1250 grams who received mechanical ventilation and surfactant 49 infants were randomized (Mariani 1997). There were no differences in the proportion of patients requiring reintubation, mortality, air leak, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, or retinopathy of prematurity. The Network SAVE trial was stopped prior to completing enrollment due to an increased incidence of gastrointestinal perforation in infants who received glucocorticoid. No adverse effects of permissive hypercarbia were seen. In a retrospective population-based study that assessed intubation practices in infants 500 to 1499 g, Goldstein (1990) reported that severe respiratory acidosis was well tolerated in five infants without adverse effects. These data suggest that reducing ventilator support early in infants undergoing mechanical ventilation is safe.

Limitations: One major limitation of the study design is that the intervention cannot be masked and usual care could change over the period of the study to become more like the LLV intervention strategy. This occurrence would bias the study results in the direction of the null hypothesis rather than toward acceptance of a potentially ineffective or harmful therapy. It would be possible to randomize centers or neonatologists to the

2 strategies, however this raises important unit of analysis questions and obviates the reduction in center and neonatologist bias obtained by randomizing infants. A second limitation is the potential difficulty in obtaining study intervention compliance among clinicians whose patients are assigned to the LLV. Network neonatologists reported in a prior survey that they were already using permissive hypercapnia, although this turned out not to be true when infant blood gases were reviewed. The survey indicates a possible willingness to accept hypercarbia when it occurs.

A third limitation is the use of gestational age entry criteria rather than birth weight entry criteria. Susceptibility to lung injury and CLD increases with decreasing maturity at birth. When available, gestational age is probably the better indicator of maturity. Certainly birth weight varies greatly at a given gestational age and other infant physical characteristics have been shown to be unreliable estimators of gestational age (Donovan, 1999). Best obstetrical estimates of gestational age may by unavailable in some infants. In order to maximize enrollment and thus minimize study duration, it is proposed that birth weight or possibly estimated fetal weight be used to assess enrollment eligibility.

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CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☐ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

☒ COMPETING CONTINUATION of grant number: 5 U10 HD27853-10
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl.only)*
☒ No ☐ Previously reported
☐ Yes. If "Yes," ☐ Not previously reported

☐ SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

☐ FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

•Human Subjects; •Vertebrate Animals; •Debarment and Suspension; •Drug-Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only);* •Lobbying; •Delinquent Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 19.)*

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

3. FACILITIES AND ADMINISTRATION COSTS (F & A)

Indicate the applicant organization's most recent F & A cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative F & A cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates,* and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. F & A costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, and specialized grant applications.

☒ DHHS Agreement dated: 05/20/98 ☐ No Facilities and Administration Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on F & A costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base $ 126,100 x Rate applied 53 % = F & A costs (1) $ 66,833

b. Entire proposed project period: Amount of base $ 667,318 x Rate applied 53 % = F & A costs (2) $ 353,678

(1) Add to total direct costs from form page 4 and enter new total on Face Page, Item 7b. Yr.2: 129,673 X 53%
(2) Add to total direct costs from form page 5 and enter new total on Face Page, Item 8b. Yr.3: 133,353 X 53%
Yr 4: 137,144 X 53%
Yr.5: 141,048 X 53%

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. SMOKE-FREE WORKPLACE

Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?

☒ Yes ☐ No *(The response to this question has no impact on the review or funding of this application.)*

AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services

691785

Follow instructions carefully.
Do not exceed character length restrictions indicated on sar

PI: **CARLO, WALDEMAR** Council: 01/2001

Grant #: ~~1 U10 HD040487-01~~

Dual: 2U10HD34216-06

IRG: ZHD1 SRC(99) Received: 07/11/2000

1. TITLE OF PROJECT

Cooperative Multicenter Neonatal Research Network

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*

Number: HD-00-010 Title: National Institute of Child Health and Human Development

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR New Investigator ☐ YES

3a. NAME *(Last, first, middle)*: Carlo, Waldemar A.

3b. DEGREE(S): MD

3c. SOCIAL SECURITY NO. Provide on Form Page KK

3d. POSITION TITLE: Director of Neonatology
Professor of Pediatrics

3e. MAILING ADDRESS *(Street, city, state, zip code)*:
University of Alabama at Birmingham
Division of Neonatology
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT: Department of Pediatrics

3g. MAJOR SUBDIVISION: School of Medicine

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 205/934-4680
FAX: 205/934-3100

E-MAIL ADDRESS: wcarlo@peds.uab.edu

4. HUMAN SUBJECTS ☐ No ☒ Yes
4a. If "Yes," Exemption no. or IRB approval date: Multiple dates
☐ Full IRB or ☐ Expedited Review
4b. Assurance of compliance no.: M1149

5. VERTEBRATE ANIMALS ☒ No ☐ Yes
5a. If "Yes," IACUC approval date
5b. Animal welfare assurance no.: A3255-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
4/01/01	3/31/06	108,568	155,795	572,448	821,462

9. APPLICANT ORGANIZATION
Name: University of Alabama at Birmingham
Address: 710 20th Street South
Birmingham, AL 35294-0111

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE: 01

12. ENTITY IDENTIFICATION NUMBER: 1636005396A6
DUNS NO. *(if available)*: 063690705

Congressional District: VI

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Maggie Casey
Title: Director, Ofc of Grants & Contracts Admin.
Address: 701 20th Street S., Suite 1170
Birmingham, AL 35294-0111
Telephone: 205/934-5266
Fax: 205?975-5977
E-mail: OGCAAPPS@provost.uab.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Joan F. Lorden, Ph.D.
Title: Associate Provost for Research
Address: 701 20th Street S. Suite 1170
Birmingham, AL 35294-0111
Telephone: 205/934-5266
Fax: 205/975-5977
E-mail: OGCAAPPS@provost.uab.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* — DATE: 6/28/00

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)* — DATE: 6/30/00

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This application provides evidence that the Division of Neonatology and the Regional Neonatal Intensive Care Unit (NICU) at the University of Alabama at Birmingham (UAB) have: 1) the clinical trial experience, 2) the qualified and motivated professional personnel, 3) a large and high-risk patient population, 4) all-inclusive facilities and resources, and 5) the broad University and medical community support to meet and exceed each of the requirements of the NICHD Cooperative Neonatal Research Network Request for Application. In addition to the active participation in the NICHD Neonatal Network studies, the Division has been involved in the design and implementation of ten multicenter and six single center randomized clinical trials during the last decade. The eight board-certified neonatologists in the Division decidedly support collaborative research and this application. An average of 945 neonates are admitted per year to the Regional NICU at UAB. The well established referral patterns from all NICUs in the region and the state-wide perinatal health care system assure a large pool of high-risk admissions for clinical research in the coming years. Strong clinical ties and ongoing collaborative clinical research projects and grants with accomplished maternal-fetal medicine specialists foster an environment conducive to excellence in perinatal trials. Collaboration with over 20 established faculty members in 12 divisions, departments, and research centers throughout the University support exceptional research. State-of-the-art facilities, talented personnel, and full clinical capabilities allow the Division to provide services for neonates with any medical or surgical disorder during hospitalization and after discharge. The comprehensive, multidisciplinary follow-up program with over 90% compliance rate assures thorough long-term evaluation and care. Existing complementary maternal and infant data bases maintained by dedicated personnel are routinely used for data retrieval, analysis, and research. Availability of three full-time experienced neonatal research nurses allows patient enrollment and protocol implementation 24 hours a day, 7 days a week. A protocol concept, based on large retrospective studies in preterm infants and randomized studies in preterm infants and adults, proposes a novel strategy for mechanical ventilation that may reduce the incidence and severity of chronic lung disease. The proposed team of investigators at UAB will work with the NICHD and the Steering Committee to design, prioritize, plan, implement, analyze, interpret, and report randomized trials and observational studies to address and resolve current and future controversies in neonatal care. The investigators believe that strict adherence to rigorously designed studies is necessary to identify optimal diagnostic, therapeutic, and management strategies. They fully support the philosophy, purpose, policies, and procedures of the Neonatal Network. The qualifications and unequivocal commitment of the Principal Investigator, Division, Department, and University will ensure superior performance if UAB is selected to continue in the Neonatal Network.

PERFORMANCE SITE(S) (*organization, city, state*)

University Hospital
University of Alabama at Birmingham
Birmingham, Alabama

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Waldemar A. Carlo, M.D.	University of Alabama at Birmingham	Principal Investigator
Joseph B. Philips, III, M.D.	University of Alabama at Birmingham	Investigator
Namasivayam Ambalavanan, M.D.	University of Alabama at Birmingham	Investigator
Robert Schelonka, M.D.	University of Alabama at Birmingham	Investigator

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APPENDICES **Page**

DD Principal Investigator/Program Director *(Last, first, middle)*: Carlo, Waldemar A.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 4/1/01 THROUGH 3/31/06

PERSONNEL *(Applicant organization only)*

NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Waldemar A. Carlo	Principal Investigator	#	%	$	7,032	1,477	8,509
Shirley Cosby	Study Coordinator				20,911	5,374	26,285
Monica Collins	Study Coordinator				31,670	8,139	39,809
Cecelia Goodgame	Data Processing				12,490	3,210	15,700
Joseph B. Philips	Investigator		(as needed)		0	0	0
N. Ambalavanan	Investigator		(as needed)		0	0	0
Robert Schelonka	Investigator		(as needed)		0	0	0
	SUBTOTALS →				72,103	18,200	90,303

CONSULTANT COSTS — 0

EQUIPMENT *(Itemize)* — 0

SUPPLIES *(Itemize by category)* Patient record supplies: Needed for daily maintenance of projects which include paper, pens, file folders, hanging folders, envelopes, mailers, note pads, clips, binders for the study coordinators, data processing specialist, and PI for a total of $600. A five drawer lateral file cabinet with lock for confidential storage of patient data collected and protocl information for exclusive use on Network projects for $916. Computer supplies: Printer cartridges for a total of $70. — 1,586

TRAVEL (@1440 per trip)
10 trips per year (4PI, 2 investigator, 4 study coordinators to Bethesda, MD) — 14,400

PATIENT CARE COSTS
INPATIENT — 0
OUTPATIENT — 0

ALTERATIONS AND RENOVATIONS *(Itemize by category)* — 0

OTHER EXPENSES *(Itemize by category)*

Paging service	$504
Copying	$500
Telephone	$745
Postage	$530

2,279

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD — $108,568

CONSORTIUM/CONTRACTUAL COSTS
DIRECT COSTS
FACILITIES AND ADMINISTRATION COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* → $108,568

= Months Dedicated to Project
% = Percentage of Effort
$ = Institutional Based Salary

DD

Principal Investigator/Program Director *(Last, first, middle)*: Carlo[redacted]aldemar A.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM | THROUGH

PERSONNEL *(Applicant organization only)*					DOLLAR AMOUNT REQUESTED *(omit cents)*		
NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
	Principal Investigator						
William Andrews	Investigator	#	(as needed)				
Richard Davis	Investigator		(as needed)				
Robert Goldenberg	Investigator		(as needed)				
John Hauth	Investigator		(as needed)				
Kathleen Nelson	Investigator		(as needed)				
Craig Ramey	Investigator		(as needed)				
Dwight Rouse	Investigator		(as needed)				
			SUBTOTALS →		0	0	0

CONSULTANT COSTS

EQUIPMENT *(Itemize)*

SUPPLIES *(Itemize by category)*

TRAVEL

PATIENT CARE COSTS — INPATIENT / OUTPATIENT

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

OTHER EXPENSES *(Itemize by category)*

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD $

CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS / FACILITIES AND ADMINISTRATION COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* → $

= Months Dedicated to Project

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD (from Form Page 4)	ADDITIONAL YEARS OF SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits Applicant organization only*		90,303	93,012	95,802	98,676	101,636
CONSULTANT COSTS		0	0	0	0	0
EQUIPMENT		0	0	0	0	0
SUPPLIES		1,586	690	711	732	754
TRAVEL		14,400	14,832	15,276	15,734	16,206
PATIENT CARE COSTS	INPATIENT	0	0	0	0	0
	OUTPATIENT	0	0	0	0	0
ALTERATIONS AND RENOVATIONS		0	0	0	0	0
OTHER EXPENSES		2,279	2,347	2,417	2,490	2,565
SUBTOTAL DIRECT COSTS		108,568	110,881	114,206	117,632	121,161
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT	0	0	0	0	0
	F&A	0	0	0	0	0
TOTAL DIRECT COSTS		108,568	110,881	114,206	117,632	121,161

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT *(Item 8a, Face Page)* → $572,448

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.
As per instructions, subsequent years reflect a 3% budgetary increase.

Personnel:
Waldemar A. Carlo, M.D. (Principal Investigator). It has been determined that a minimum of [%] effort will be required of the PI to direct the project. Dr. Carlo's biographical sketch as well as his previous role as PI on the Multicenter Neonatal Research Network and similar projects (documented in the Neonatology Staffing Section) provides conclusive evidence of his effort to ensure the success of UAB's participation in the Neonatal Research Network.

Shirley Cosby, RN, BSN (Study Coordinator). Ms Cosby will commit [%] of her effort to the activities of the Neonatal Research Network to ensure the success of the ongoing research at this institution. Ms. Cosby's commitment of time the last two years has proven to be invaluable in patient enrollment, protocol compliance, and data collection.

Monica Collins, RN, BSN, MaEd (Study Coordinator). Ms. Collins will commit [%] of her effort to the research activities of the Network. Her previous 10 years experience as a research coordinator in the Division of Neonatology will assure the success of this project. She will share all the duties of the Study Coordinator with Ms. Cosby.

Cecelia Goodgame (Data Processing Specialist). Ms. Goodgame will devote [ ] hours per week of her effort to the timely and accurate entry and transmission of collected data.

Equipment:

A five drawer lateral file cabinet with lock for confidential storage of patient data collected and protocol information can be purchased for $916 from Church and Stagg Supply Company for exclusive use on Network projects.

Supplies:

Office supplies needed for daily maintenance of project which include paper, pens, file folders, hanging folders, letterhead, envelopes, mailers, note pads, clips and binders provided for the study coordinators, data processing specialist, and PI for a total of $600.

Computer supplies needed for use by the Network provided computer include printer cartridges for a total of $70.

Travel:

Travel between Birmingham and Bethesda, MD is requested for ten round trips according to the specifications of the RFA. Included is round-trip airfare (government contract); weekday travel is $990, hotel in the area quote an average of $150 per night, while $75 is allowed for meals and local travel per day. Expenses listed are based on a two night meeting total of $1440 per trip.

Other expenses:

Beeper leasing is necessary to allow rapid access to the study coordinators. This assures seven days a week, 24 hours a day availability for enrollment or should problems or questions arise ($21/month x 2 x 12 =$504).

Copy services are necessary for literature searches, data forms, correspondence, statistics, all communications from NICHD and Data Center, and distribution among members of the research team ($500).

A dedicated telephone line for modem use for communications with the Data Center ($21.25 per month/$255 annual fees). The remainder of $500 is based on experience gathered through our previous participation in the Network and includes long distance calls and fax transmissions to the NICHD, the Data Center, and other sites.

Postage and express mail fees are estimated at $530 per year based on experience gathered through our previous participation in the Network. These expenses tend to be incurred regularly with shipping materials, samples, and correspondence to the NICHD, the Data Center, and other sites.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
William W. Andrews, Ph.D., M.D.	Professor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Auburn University, Auburn, Alabama	B.S.	1974	Chemistry
University of Texas Health Sci. Ctr. at Dallas, Texas	Ph.D.	1980	Physiology
Univ. of Alabama School of Medicine	M.D.	1984	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1976-1980 NIH Predoctoral Fellow, Department of Physiology, University of Texas Health Science Center at Dallas.
1984-1988 Resident Physician, Department of Obstetrics and Gynecology, University of Alabama Hospitals, Birmingham, Alabama
1988-1990 Fellow in Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Parkland Memorial Hospital, Dallas, Texas.
1990-1995 Assistant Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham
1990-Present Director, Obstetrics and Gynecology Infectious Disease Research Laboratory, University of Alabama at Birmingham
1995-Present Associate Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham
1999-Present Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham

Honors:

Sigma Xi, 10th Annual Graduate Student Research Forum Award, 1977; National Dean's List, University of Alabama School of Medicine, 1981-1982; E.L. Gibson Foundation Scholarship Recipient, University of Alabama School of Medicine, 1980-1983; Alpha Omega Alpha Medical Honor Society 1982; Award for Superior Achievement in the Clinical Curriculum, University of Alabama School of Medicine, 1984; J. Marion Sims Award for Outstanding abilities in Obstetrics and Gynecology, Best Senior Resident Presentation in Obstetrics and Gynecology, Resident Research Day, 1987; Chief Resident in Obstetrics and Gynecology, University of Alabama at Birmingham, 1987-1988; Best Teaching Chief Resident, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 1988. Best Poster Award, Session V. Society of Perinatal Obstetricians Annual Meeting, San Francisco, CA, 1993. National Faculty Award for Excellence in Resident Education in Obstetrics and Gynecology, 1994.

Selected Publications:

Rouse DJ, **Andrews WW**, Goldenberg RL, Owen J: Screening and treatment of asymptomatic bacteriuria of pregnancy to prevent pyelonephritis: a cost effectiveness and cost-benefit analysis. Obstet Gynecol 86:119-23, 1995.

Andrews WW, Hauth JC, Goldenberg RL, Mazur M, Gomez R, Romero R, Cassell G: Amniotic fluid IL-6: Correlation with chorioamnion colonization and gestational age in women delivered following spontaneous labor versus indicated delivery. Am J Obstet Gynecol 173:606-12, 1995.

Wenstrom KD, **Andrews WW**, Maher JE: Amnioinfusion survey: Prevalence, protocols, and complications. Obstet Gynecol 86: 572-6; 1995.

Meis PJ, Goldenberg RL, Mercer B, Moawad A, Das A, McNellis D, Johnson F, Iams JD, Thom E, **Andrews WW**, and the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network: The preterm prediction study: Significance of vaginal infections. Am J Obstet Gynecol 173: 1231-5; 1995.

Andrews WW, Goldenberg RL, Hauth JC: Preterm labor: Emerging role of genital tract infections. Inf Agents Dis 4:196-211; 1995.

Hauth JC, Goldenberg RL, **Andrews WW**, DuBard MB, Copper RL: Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med 333:1732-6, 1995.

Guinn DA, Goldenberg RL, Hauth JC, **Andrews WW**, Thom E, Romero R: Risk factors for the development of preterm premature rupture of the membranes following arrest of preterm labor. Am J Obstet Gynecol 173:1310-5, 1995.

Goldenberg RL, **Andrews WW**: Intrauterine infection and why preterm prevention programs have failed. Health. Am J Public Health 86:781-2, 1996.

Parker CR, Atkinson MW, Owen J, **Andrews WW**: Dynamics of the fetal adrenal, cholesterol and apolipoprotein B responses to antenatal betamethasone therapy. Am J Obstet Gynecol 174:562-5. 1996.

Goldenberg RL, Klebanoff MA, Nugent R, Krohn MA, Hillier S, **Andrews WW**, The VIP Study Group. Bacterial colonization of the vagina during pregnancy in four ethnic groups. Am J Obstet Gynecol 174:1618-21, 1996.

Wenstrom KD, **Andrews WW**, Tamura T, DuBard MB, Johnston KE, Hemstreet GP: Elevated amniotic fluid interleukin-6 levels at genetic amniocentesis predict subsequent pregnancy loss. Am J Obstet Gynecol 175:830-3, 1996.

Rouse DJ, Hauth JC, **Andrews WW**, Mills BB, Maher JE: Chlorhexidine vaginal irrigation for the prevention of peripartal infection: A placebo-controlled randomized clinical trial. Am J Obstet Gynecol 176:617-22, 1997.

Andrews WW, Lee H, Roden WJ, Mott CW: Detection of genitourinary tract chlamydia infection in pregnant women by ligase chain reaction assay. Obstet Gynecol 89:556-60, 1997.

Goldenberg RL, **Andrews WW**, Yuan A, MacKay T, St. Louis M. Sexually transmitted diseases and adverse outcomes of pregnancy. Clin Perinatol 24:23-41, 1997

Goepfert AR, Guinn DA, **Andrews WW**, Hauth JC: Necrotizing fasciitis following cesarean delivery. Obstet & Gynecol 89:409-12, 1997.

Peaceman AM, **Andrews WW**, Thorpe JM, Cliver SP, Lukes AE, Iams JD, Coultrip L, Eriksen N, Holbrook H, Elliott J, Ingardia C, Pietrantoni M. Fetal fibronectin as a predictor of preterm birth in symptomatic patients - a multi center trial. Am J Obstet Gynecol 14:13-18, 1997.

Hensleigh P, **Andrews WW**, Brown Z, Greenspoon J, Yasukawa L, Heurta K, Prober C: Primary genital herpes infection is rare in pregnancy women presenting with first episode genital lesions. Obstet Gynecol 89:891-95, 1997

Tamura T, **Andrews WW**, Hemstreet GP, Johnson KE: Comparative performance of commercially available elisa kits for the measurement of interleukin-6 in amniotic fluid. Dis Obstet Gynecol 1997;5:222-225.

Hauth JC, **Andrews WW**, Goldenberg RL. Infection-related risk factors predictive of spontaneous preterm labor and birth. Prenat Neonat Med 1998;3:86-90.

Goldenberg RL, **Andrews WW**, Hauth JC. Markers of Preterm Birth. Prenatal and Neonatal Med 1998;3:43-46.

Wenstrom KD, Hauth JC, DuBard MB, **Andrews WW**, Goldenberg RL, Cliver SP: Elevated second trimester amniotic fluid interleukin-6 levels predict preterm delivery. Am J Gynecol 1997; 178:546-550

Kimberlin, DF, **Andrews WW**. Bacterial Vaginosis: Association with adverse pregnancy outcome. Seminars in Perinatol 1998; 22:242-250.

Andrews WW, Gilstrap LC III: Urinary tract infections in pregnancy. In: Gleicher N (ed). Principles of Medical Therapy in Pregnancy. 3rd Ed. Appleton & Lange, East Norwalk, CT,1998 pp 1052-1063.

Rouse DJ, **Andrews WW**, Lin FYC, et al. Antibiotic susceptibility profile of vertically acquired Group B streptococcus. Obstet Gynecol, 1998;92:931-4.

Wenstrom KD, **Andrews WW**, Bowles N, Towbin JA, Hauth JC, Goldenberg RL. Intrauterine viral infection at the time of second trimester genetic amniocentesis is not associated with post-procedure pregnancy loss. Obstet Gynecol, 1997;92:320-4.

Kimberlin DF, **Andrews WW**. Pharmacokinetics of valaciclovir in late pregnancy. Am J Obstet Gynecol, 1998;179:846-851.

Andrews WW, Tsao, J, Goldenberg RL, Hauth JC, Mercer B, Iams JD, Meis P, Moawad A, Das A, Van Dorsten PJ, Caritis SN, Thurnau G, Miodovnik M, Roberts J, McNellis D, and the National Institute for Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: cervical sialidase is associated with bacterial vaginosis, but not spontaneous preterm birth. Am J Obstet Gynecol, 1999;180:1151-54.

Ebrahim S, Levine W, Zaidi A, **Andrews WW**, DuBard M, MacKay T, Groseclose S, St. Louis M, Hauth J, Goldenberg R, Fleenor M: Syphilis, gonorrhea and drug abuse among pregnant women in Jefferson County, Alabama, US,1980-1994: Monitoring epidemic trends through systematically collected health services data. STI 1999;75(5) 300-305.

Richter HE, Holley RL, **Andrews WW**, Owen J, Miller KB. The association of Interleukin-6 with clinical and laboratory parameters of acute pelvic inflammatory disease Am J Obstet Gynecol, 1999;181:940-4.

Goepfert AR, Goldenberg RL, **Andrews WW**, Hauth JC, Mercer B, Iams J, Meis P, et al. The Preterm Prediction Study: Quantitative fetal fibronectin values and the prediction of spontaneous preterm birth. (In Press) Am J Obstet Gynecol, 1999.

Andrews WW, Copper RL, Hauth JC, Goldenberg RL, Neely C, Ellis J, DuBard MB. Mid-trimester cervical ultrasound findings predict early spontaneous delivery. Am J Obstet Gynecol 2000;95:222-6.

Goldenberg RL, **Andrews WW**, Guerrant RL, et al. The Preterm prediction study: Cervical lactoferrin, other markers of lower genital tract infection, and preterm birth. Am J Obstet Gynecol, 2000;182(3):631-5.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.

Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Namasivayam Ambalavanan, M.D.	Clinical Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
JIPMER, Pondicherry, India	M.B.,B.S.	1988	Medicine
PGIMER, Chandigarh, India	M.D. (Ped)	1993	Pediatrics
University of Alabama at Birmingham, AL	Fellowship	1993-1997	Neonatology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

1993 - 1997	Fellow, Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL, USA
1998-present	Clinical Asst. Prof, Div. of Neonatology, University of Alabama at Birmingham, Birmingham, AL, USA
2000-present	Assistant Prof, Div. of Neonatology, University of Alabama at Birmingham, Birmingham, AL, USA

HONORS AND AWARDS:

Young Investigator Award- Southern Society of Pediatric Research 2000
Finalist for Basic Science Young Investigator Award- Southern Society of Pediatric Research 1997, 1998, 2000
Trainee Travel Award Southern Society of Pediatric Research 1995
Wyeth Pediatrics Neonatology Research Fund: grant 1995-1996
Chairman's Award May 1997

SELECTED PEER REVIEWED PUBLICATIONS:

1. Rayyis SF, **Ambalavanan N**, Wright L, Carlo WA: Randomized trial of "Slow" vs. "Fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. J Pediatr 134(3):293-297, 1999
2. **Ambalavanan N**, Carlo WA: Analgesia for ventilated neonates: Where do we stand? J Pediatr 135(4):403-405, Oct 1999
3. **Ambalavanan N**, Bulger A, Philips JB III: Hypoxia-induced release of peptide growth factors from neonatal porcine pulmonary artery smooth muscle cells. Biol Neonate 76(5):311-319, Nov 1999
4. **Ambalavanan N**, Mariani G, Bulger A, Philips JB III: Role of Nitric Oxide in Regulating Neonatal Porcine Pulmonary Artery Smooth Muscle Cell Proliferation. Biol Neonate 76(5):291-300, Nov 1999
5. **Ambalavanan N**, Nelson K, Alexander G, Carlo WA: Prediction of neurologic morbidity in ELBW infants ***(Accepted for publication by J Perinatol).***

SUBMITTED:

1. **Ambalavanan N**, Carlo WA: Prediction of extremely low birth weight (ELBW) neonatal mortality by neural networks and logistic regression.
2. **Ambalavanan N**, Carlo WF, Bulger A, Shi J, Philips JB III: The effect of cigarette smoke extract on neonatal vascular smooth muscle cells.
3. **Ambalavanan N**, Bulger A, Ware J, St.John E, Philips JB III: Hemodynamic efficacy and feasibility of nitric oxide administration by oxygen hood in a neonatal porcine model of hypoxia- and group B streptococcal-induced pulmonary hypertension.
4. **Ambalavanan N**, Bulger A, Ware J, Philips JB III: Hemodynamic effects of the K ATP channel agonist levcromakalim in hypoxia- and group B streptococcus-induced neonatal porcine pulmonary hypertension.

ABSTRACTS:

Abstracts (all accepted for presentation except #14&23):

1. **Ambalavanan N**, Philips JB IV, Bulger A, Philips JB III: The Effect of pH on Neonatal Pulmonary Artery Smooth Muscle and Endothelial Cell Proliferation. J Investig Med 43(1): 44A, Feb 1995
2. **Ambalavanan N**, Bryant L, Bulger A, Philips JB III: Nitric oxide donors inhibit neonatal pulmonary artery smooth muscle cell proliferation. Pediatr Res 37(4): 324 A, April 1995
3. **Ambalavanan N**, Bulger A, Philips JB III: Hypoxia increases vascular endothelial growth factor production by neonatal pulmonary artery smooth muscle cells. Pediatr Res 37(4): 324 A, April 1995
4. **Ambalavanan N**, Bulger A, Philips JB III: The effect of pH on neonatal pulmonary artery smooth muscle and endothelial cell proliferation. Pediatr Res 37(4): 325 A, April 1995
5. **Ambalavanan N**, Bulger A, Philips JB III: Does a heme protein regulate hypoxia-mediated changes in neonatal pulmonary artery smooth muscle cell proliferation? J Investig Med 45(1): 67A, Jan 1997
6. **Ambalavanan N**, Bulger A, Philips JB III: Hypoxia-mediated release of peptide growth factors from neonatal pulmonary artery smooth muscle cells. J Investig Med 45(1): 21A, Jan 1997
7. **Ambalavanan N**, Bulger A, Philips JB III: Hypoxia-mediated release of peptide growth factors from neonatal pulmonary artery smooth muscle cells. Pediatr Res 41(4): 245A, April 1997
8. **Ambalavanan N**, Bulger A, Philips JB III: Does a heme protein regulate hypoxia-mediated changes in neonatal pulmonary artery smooth muscle cell proliferation? Pediatr Res 41(4): 244A, April 1997
9. **Ambalavanan N**, Bulger A, Philips JB III: Regulation of neonatal pulmonary artery smooth muscle cell proliferation by nitric oxide. Pediatr Res 41(4): 244A, April 1997
10. Mariani G, **Ambalavanan N**, Bulger A, Philips JB III: Prostaglandin E1 and peptide growth factors stimulate neonatal pulmonary artery smooth muscle cell proliferation in a synergistic manner. Pediatr Res 41(4): 260A, April 1997
11. Rayyis S, **Ambalavanan N**, Wright L, Carlo WA: Randomized trial of "Slow" versus "Fast" feeding advancement in very low birthweight infants. Pediatr Res 41(4): 172A, April 1997
12. **Ambalavanan N**, Bulger A, Philips JB III: Hypoxia-inducible factor-1 (HIF-1) does not mediate hypoxic inhibition of neonatal pulmonary artery smooth muscle cell proliferation. J Investig Med 46(1): 23A, Jan 1998
13. **Ambalavanan N**, Bulger A, Philips JB: Hypoxia-mediated alterations of signal transduction pathways in neonatal pulmonary artery smooth muscle cells. Pediatr Res 43(4): 273A, April 1998
14. **Ambalavanan N**, Carlo WA: Prediction of mortality in ELBW infants using logistic and linear regression versus neural networks. Pediatr Res 43(4): 205A, April 1998
15. **Ambalavanan N**, Nelson K, Alexander G, Carlo WA: Prediction of neurologic morbidity and its determinants in ELBW infants. Pediatr Res 43(4): 205A, April 1998
16. Carlo WF, **Ambalavanan N**, Bulger A, Philips JB III: The effect of cigarette smoke extract on neonatal pulmonary artery smooth muscle cell proliferation. J Investig Med 47(2): 141A, Feb 1999
17. **Ambalavanan N**, Carlo WF, Bulger A, Shi J, Philips JB III: Cigarette smoke extract causes non-apoptotic cell death in neonatal vascular smooth muscle cells. Pediatr Res 45(4):294A, Apr 1999
18. **Ambalavanan N**, Carlo WA: Prediction of extremely low birth weight (ELBW) neonatal mortality by neural networks and logistic regression. Pediatr Res: 236A, Apr 1999
19. Philips JB, **Ambalavanan N**, Ware J, Bulger A, Lin B, Pritchard DG: Group B Streptococcal Hyaluronidase Does Not Increase Systemic Bacterial Invasion in a Neonatal Rat Pup Model. Pediatr Res 272A, Apr 1999
20. **Ambalavanan N**, Bulger A, Ware J, St.John E, Philips JB III: Nitric oxide administration by oxygen hood in neonatal pulmonary hypertension. J Investig Med 48(1): 134A, Jan 2000
21. **Ambalavanan N**, Bulger A, Ware J, Philips JB III: ATP-gated potassium channels in neonatal pulmonary hypertension. J Investig Med 48(1): 152A, Jan 2000
22. Carlo WF, Villamor EI, **Ambalavanan N**, DeMey JG, Blanco C: Chronic exposure to cigarette smoke extract impairs endothelium-dependent vasodilation of chick embryo pulmonary arteries. Pediatr Res Pediatr Res 47(4): 353A, Apr 2000
23. **Ambalavanan N**, Bulger A, Ware J, Philips JB III: ATP-gated potassium channels in neonatal pulmonary hypertension. Pediatr Res 47(4): 350A, Apr 2000
24. **Ambalavanan N**, Bulger A, Ware J, St.John E, Philips JB III: Nitric oxide administration by oxygen hood in neonatal pulmonary hypertension. Pediatr Res 47(4): 350A, Apr 2000
25. Haberman B, Donovan E, **Ambalavanan N**, Hansen N, Vohr B, and the NICHD Neonatal Research Network Follow-up Subcommittee: Follow-up Compliance of Newborn Intensive Care Unit (NICU) Survivors. Pediatr Res 47(4): 312A, Apr 2000

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Monica Vogt Collins	Clinical Research Nurse

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Alabama at Birmingham	BSN	1981	Nursing
University of Alabama at Birmingham	MaEd	1983	Agency Counseling

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

1981-1983 Staff Nurse – Regional Newborn Intensive Care Unit, University Hospital, Birmingham, Alabama
1983-1986 Perinatal Family Liaison, University Hospital, Birmingham, Alabama
1986-present Clinical Research Coordinator, University of Alabama at Birmingham, Birmingham, Alabama

PUBLICATIONS:

Braune K, **Collins M**, and Young, M. ed: Perinatal Asphyxia. NAACOG's Clinical Issues in Obstetrics, Gynecologic and Neonatal Nursing, April 1991.

Collins M, and Braune K. Administration Practices Vary from Different Surfactant Preparations. Journal of Obstetrics, Gynecologic and Neonatal Nursing, Vol 19, No. 6, p. 467 (Letter to the Editor).

Cassady G, Crouse D, Kirklin JW, Strange M, Joiner C, Godoy G, Odresin G, Cutter G, Kirklin JK, Pacifico A, **Collins M,** Lell W, Satterwhite C, and Philips J. A Randomized Controlled Trial of Very Early Prophylactic Ligation of the Ductus Arteriosus in Babies Who Weigh 1000 Grams or Less at Birth. New England Journal of Medicine, May 1989.

Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Archives of Ophthalmology, Vol. 106, 1988, pp.471-479.

Cryotherapy for Retinopathy of Prematurity Cooperataive Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Pediatrics, Vol. 81, 5:697-796, 1988.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Waldemar A. Carlo, MD	Professor and Division Director

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Univ. of Puerto Rico, Mayaguez, P.R.	B.S.	1975	Biology
Univ. of Puerto Rico Med Sci Campus, San Juan, P.R.	M.D.	1977	Medicine
Univ Children's Hospital, P.R. Med Ctr, San Juan, P.R	Residency	1977-79	Pediatrics
Univ Children's Hospital, P.R. Med Ctr, San Juan, P.R	Chief Resident	1979-80	Pediatrics
Rainbow Babies & Child Hosp., Cleveland, Ohio	Fellowship	1980-82	Neonatology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO**

PROFESSIONAL EXPERIENCE:

1982 - 1989	Asst Prof of Pediatrics, Case Western Reserve Sch of Med, Cleveland, Ohio
1984 - 1990	Asst Prof of Reproductive Biology, CWRU Sch of Med, Cleveland, Ohio
1986 - 1990	Assoc Dir, NICU, Rainbow Babies & Children's Hospital, Cleveland, Ohio
1989 - 1990	Assoc Prof of Pediatrics, Case Western Reserve Sch of Med, Cleveland, Ohio
1991 - present	Professor of Pediatrics, Univ of Alabama at Birmingham, Birmingham, AL
1991 - present	Dir, Division of Neonatology, Dir of Nurseries, Univ of Alabama at Birmingham, Bham, AL
1998 - present	Co-Chairperson Neonatal Resuscitation Program, American Academy of Pediatrics

RESEARCH AWARDS:

PI, NHLBI, "Respiratory Control of the Alae Nasi in Preterm Infants," 1983-1986
Co-PI, NHLBI, "Respiratory Muscle Responses to Neurochemical Stimuli in Infants," 1987-1991
PI, NICHD, "Randomized Clinical Trial of High and Low Umbilical Artery Catheter Placement," 1989-1991
PI, BIG SOD, "The Safety and Efficacy of r-h CuZnSOD to Prevent BPD," 1997-1998
PI, Alabama Department of Public Health, "Perinatal Outreach Education Grant," 1991-2001
Co-PI, NIH, "PERC, UAB Rural Perinatal Center: Infection and Prematurity - Project IV," 1996 - 2001
PI, NICHD, "Cooperative Multicenter Neonatal Research Network," 1996-2001

SELECTED PEER REVIEWED PUBLICATIONS: (Selected from 91 peer reviewed publications):

The HIFI Study Group: High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 320:88-93, 1989.

Carlo WA, and DiFiore JM: Respiratory muscle responses to changes in chemoreceptor drive in infants. J. Appl Physiol 68:1041-1047, 1990.

Carlo WA, Siner B, Chatburn RL, Robertson S, and Martin RJ: Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome. J Pediatr 117:765-770, 1990.

The HIFI Study Group: High frequency oscillatory ventilation compared with conventional mechanical ventilation in treatment of respiratory failure in preterm infants: Assessment of pulmonary function at 9 months of corrected age. J Pediatr 116:933-941.

The HIFI Study Group: High frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: Neurodevelopmental status at 16 and 24 months. J Pediatr 117:939-946, 1990.

Miller MJ, DiFiore JM, Strohl KP, **Carlo WA**, and Martin RJ: Effects of CO_2 rebreathing on pulmonary mechanics in premature infants. J Appl Physiol 70:2582-2586, 1991.

Carlo WA, and Chatburn RL: "Expert system" for assisted ventilation in infants with respiratory distress syndrome. Dev Physiopathol C1 2:173-178, 1991.

Umbilical Artery Catheter Trial Study Group: Relationship of intraventricular hemorrhage or death with the level of umbilical artery catheter placement: A multicenter randomized clinical trial. Pediatrics 90:881-887, 1992.

Haywood JL, Goldenberg RL, Bronstein J, Nelson KG, **Carlo WA**: Comparison of perceived and actual rates of survival and freedom from handicap in premature infants. Am J Obstet Gynecol 171:432-439, 1994.

Cifuentes J, Myles CT, Nieves B, Carlo WA, Matalon S: Interaction of pulmonary surfactants with reactive oxygen and nitrogen species. J Appl Physiol 78:1800-1805, 1995.

Cattarossi L, Haxhiu-Poskurica B, Haxhiu MA, Litmanovitz I, Martin RJ, Carlo WA: Carotid bodies and ventilatory response to hypoxia in aminophylline treated piglets. Pediatr Pulmonol, 20:94-100, 1995.

Bronstein JM, Capilouto E, **Carlo WA**, Haywood JL, Goldenberg RL: Access to neonatal intensive care for low birth weight infants: The role of maternal characteristics. Am J Public Health 85:357-361, 1995.

Nieves-Cruz B, Rivera A, Cifuentes J, Pataki G, Matalon S, **Carlo WA**, Tanswell AK, Freeman B: Clinical surfactant preparations mediate superoxide dismutase and catalase uptake by type II cells and lung tissue. Am J Physiol, 270:L659-L667, 1996.

Mariani G, Barefield ES, and **Carlo WA**: The role of nitric oxide in the treatment of neonatal pulmonary hypertension. Current Opinion in Pediatrics, 8:118-125, 1996.

Faye-Petersen O, Johnson WH, **Carlo WA**, Pacifico AD, Blair HC: Prostaglandin E1-induced hyperostosis: Clinicopathologic correlations and possible etiopathogenetic mechanisms. Pediatr Path Lab Med, 16:489-507, 1996.

Barefield ES, Karle VA, Philips JB, III, **Carlo WA**: Inhaled nitric oxide in term infants with hypoxemic respiratory failure. J Pediatr, 129:279-286, 1996.

Bloom BT, Kattwinkel J, Hall RT, Delmore PM, Egan EA, Trout R, Malloy MH, Brown DR, Holzman IR, Coghill CH, **Carlo WA**, Pramanik AK, McCaffree MA, Toubas PL, Laudert S, Gratny LL, Weatherstone KB, Seguin JH, Willett LD, Gutcher GR, Mueller DH, and Topper WH: Comparison of Infasurf (calf lung surfactant extract) to Survanta (Beractant) in treatment and prevention of respiratory distress syndrome. Pediatrics 100:31-38, 1997.

Davis JM, Rosenfeld W, Richter SE, Parad R, Gewolb IH, Spitzer A, **Carlo W**, Couser R, Price A, Flaster E, Kassem N, Edwards L, Tierney J, and Horowitz S: Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intratracheally to premature infants with respiratory distress syndrome. Pediatrics 100:24-30, 1997.

Haywood JL, Morse S, Goldenberg RL, Bronstein J, Nelson K, **Carlo WA**: Estimation of outcome and restriction of interventions in neonates. Pediatrics 102:e20, 1998.

Bloom BT, Cohen M, Myers MM, Egan EA, Kattwinkel J, Delmore P, Hall RT, Malloy MH, Holzman IR, **Carlo WA**, Pramanik AK, McCaffree MA, Willett LD, Topper WH. Increased survival in low birthweight neonates given prophylactic surfactant. J Perinatol 18:431-435, 1998.

Tyson JE, Wright LL, Oh W, Kennedy K, Mele L, Ehrenkranz RA, Stool B, Lemons JA, Stevenson DK, Bauer CR, Korones SB, Fanaroff AA, Donovan EF, **Carlo WA**, Shankaran S, Stark AR, Papile LA, Jobe A, Stacewicz-Sapuntzakis M, Verter J. Vitamin A supplementation for extremely-low-birth-weight infants. NEJM 340: 1962-1968,1999.

Rayyis SF, Ambalavanan N, Wright L, **Carlo WA**. Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. J Pediatr. 134:293-297, 1999.

Mariani G, Cifuentes J, **Carlo WA**. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 104:1082-1088,1999.

Ambalavanan N, **Carlo WA**. Analgesia for ventilated neonates: Where do we stand. J Pediatr (editorial) 135:403-405,1999.

Carlo WA, Ambalavanan N. Conventional mechanical ventilation: traditional and new strategies Pediatr Rev 20:e117-126, 1999.

Morse SB, Haywood MD, Goldenberg RL, Bronstein J, Nelson KG, **Carlo WA**. Estimation of neonatal outcome and perinatal therapy utilization. Pediatrics 105:1046-1050, 2000.

Pending Publication

Carlo WA: Gentle Ventilation and permissive hypercapnia in neonates. Perspect Neonatal 1:4-16, 2000.

BOOKS:

Carlo WA and Chatburn RL. Neonatal Respiratory Care. Year Book Medical Publishers, Chicago, 1988.

Boynton B, **Carlo WA**, Jobe A (eds). New Therapies for Neonatal Respiratory Failure: A Physiologic Approach, Cambridge University Press, Cambridge England, 1994.

Carlo WA (ed) Neonatal Resuscitation Textbook, Spanish Edition. American Academy of Pediatrics/American Heart Association, 1997.

Neonatal Resuscitation Textbook, English Edition, American Academy of Pediatrics/American Heart Association, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Shirley S. Cosby, RN	Clinical Research Nurse

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Gadsden State Junior College, Gadsden, AL		1988	Undergraduate studies
University of Alabama at Birmingham, AL	BSN	1992	Nursing

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

1989-1990	Nursing Assistant, Holy Name of Jesus, Gadsden, Alabama
1990-1992	Perinatal Nurse Technician, University of Alabama at Birmingham, Birmingham AL
1993-1997	Critical Care Transport Nurse, University of Alabama at Birmingham, Birmingham, AL
1992-1997	Staff Nurse, University of Alabama at Birmingham, Alabama, AL
1999 – present	Supplemental Staff Nurse, University of Alabama at Birmingham, Birmingham, AL
1997 – present	Clinical Research Nurse, University of Alabama at Birmingham, Birmingham, AL

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Richard O. Davis, M.D.	Professor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Emory University, Atlanta, Georgia	B.A.	1969	
Medical College of Georgia, Augusta, Georgia	M.D.	1973	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1973-1977 Resident Physician, Department of Obstetrics and Gynecology, University of Alabama Hospitals, Birmingham, Alabama

1979-1981 Fellow in Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama

1977-1982 Assistant Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham

1982-1987 Associate Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham, Birmingham, Alabama

1987-Present Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham

1991-Present Chairman, Department of Obstetrics and Gynecology, Cooper Green Hospital, Birmingham, Alabama

1997-Present Division Director, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham, Birmingham, Alabama

2000 – Present Vice Chairman for Community Outreach and Departmental Development, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham, Birmingham, Alabama

Selected Publications:

Brumfield CG, Guinn DA, **Davis RO**, Owen J, Wenstrom KD, Mize P. The significance of a nonvisualized fetal bladder during an ultrasound examination to evaluate second trimester oligohydramnios. Ultrasound Obstet Gynecol 8:186-191, 1996.

Wenstrom KD, Owen J, **Davis RO**, Brumfield CG. Prognostic values of unexplained elevated amniotic fluid and maternal serum alpha-fetoprotein. Obstet Gynecol 87:213-6, 1996

Brumfield CG, Lin S, Conner W, Cosper PC, **Davis RO**, Owen J. Genetic amniocentesis at 11-14 weeks' versus 16-19 weeks' gestation (Won Award at 1993 Resident Research Day) Obstet Gynecol 88:114-8, 1996.

Brumfield CG, **Davis RO**, Cosper P, Owen J: Pregnancy Outcome Following Amniocentesis at 11-14 versus 16-19 Weeks' Gestation. Obstet Gynecol 88;638-9, 1996 (Letter to the Editor)

Brumfield CG, Wenstrom KD, **Davis RO**, Owen J, Cosper R. Fetal cystic hygroma: prognosis of septated versus non-septated lesions. Obstet Gynecol 88:979-982, 1996

Wenstrom KD, Owen J, Brumfield CG, **Davis RO**, DuBard M. Significance of a false positive trisomy 18 multiple marker screening test. Obstet Gynecol 90:938-42, 1997.

Wenstrom KD, Owen J, Brumfield CG, **Davis RO**, DuBard M, Garcia T. Significance of a False Positive Trisomy 18 (T18) Multiple Marker Screening Test (MMST). Obstet Gynecol 1997;90:938-42.

Brumfield CG, **Davis RO**, Owen J, Wenstrom KD, Mize P. Pregnancy outcomes following sonographic nonvisualization of the fetal stomach. Obstet Gynecol 91:905-8, 1998.

Wenstrom KD, Owen J, Brumfield CG, **Davis RO**, Dubard M. Significance of a False Positive Trisomy 18 Multiple Marker Screening Test. Obstet Gynecol, 1998; 91:636-7 (Letter to the Editor).

Brumfield CG, Wenstrom KD, Owen J, **Davis RO**. Ultrasound Findings and Multiple Marker Screening in Trisomy 18. Obstet Gynecol, 2000;95:51-4.

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Give the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Robert L. Goldenberg, M.D.	Charles E. Flowers Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(S)	FIELD OF STUDY
Columbia University, New York	B.S.	1964	History & Economics
Duke University School of Medicine, NC	M.D.	1968	Internship/Medicine
Columbia University, New York		1969-1970	Residency/OB-GYN
National Institutes of Health		1970-1972	Reproductive Medicine
Yale University, New Haven, CT		1972-1974	Residency/OB-GYN

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE

1974-1976 Assistant Professor OB/GYN, Yale University
1976-1978 Assistant Professor OB/GYN, University of Alabama at Birmingham
1977-1981 Director, Bureau of Maternal and Child Health, Alabama Department of Public Health, Montgomery, Alabama
1978-1983 Associate Professor, OB/GYN, University of Alabama at Birmingham
1983-present Professor, OB/GYN, University of Alabama at Birmingham
1989-present Professor, School of Public Health, University of Alabama at Birmingham
1988-present Charles E. Flowers Professor of Obstetrics and Gynecology
1986-1988 Congress of the United States, Office of Technology Assessment, Child Health Advisory Panel, Washington, D.C.
1986-1990 NIH, U.S. Depart. of Health and Human Serv., Expert Panel On The Content of Prenatal Care
1990-1995 Maternal and Child Health Research Committee of the NICHD
1993-1994 Consensus Development Panel on the Effect of Corticosteroids on Perinatal Outcomes, NIH
1995-1999 Chairman, Department OB-GYN, University of Alabama at Birmingham
1995-1999 Council-NICHD
1995-present Member, Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.
1997-present Institute of Medicine
1998-present Institute of Medicine Membership Committee, Obstetrics/Pediatrics Section Leader
1999-present Institute of Medicine Committee for Improving Birth Outomes in Developing Countries
1999-present Scholar, John J. Sparkman Center for International Public Health Education

PUBLICATIONS (FROM A TOTAL OF 293)

Goldenberg RL, Grodin JM, Rodbard D, et al. Gonadotropins in Women with Amenorrhea. Am J Obstet Gynecol 1973;116:1003-12.

Goldenberg RL, Nelson KG. Iatrogenic Respiratory Distress Syndrome. Am J Obstet Gynecol 1975;123:617-20.

Nelson KG, Goldenberg RL. Sex Hormones and Congenital Malformations: A Review. J Med Assoc State AL 1977;46:11-31.

Goldenberg RL, Nelson KG. Viability and the Premature Fetus in Distress. Lancet 1978;1:764-65.

Goldenberg RL, Nelson KG, Dyer RL, et al. The Variability of Viability: The Effect of Physicians' Perceptions of Viability on the Survival of Very Low Birth Weight Infants. Am J Obstet Gynecol 1982;678:143.

Goldenberg RL, Nelson KG, Davis RO. Delay in Delivery: The Influence of Gestational Age and the Duration of Delay on Improvement in Intact Survival. Obstet Gynecol 1984;64(4):480-84.

Goldenberg RL, Davis RO, Copper RL, et al. The Alabama Preterm Birth Prevention Project. Obstet Gynecol 1990;75:933-39.

Tucker JM, Goldenberg RL, Davis RO, et al. Etiologies of Preterm Birth in an Indigent Population: Is Prevention a Logical Expectation? Obstet Gynecol 1991;77:343-47.

Groome LJ, Goldenberg RL, Cliver SP, et al. Neonatal Periventricular-Intraventricular Hemorrhage After Maternal β-Sympathomimetic Tocolysis. Am J Obstet Gynecol 1992;167:873-79.

Gaudier FL, Goldenberg RL, Nelson KG, et al. Acid-base Status at Birth and Subsequent Neurosensory Impairment in Surviving 500 to 1000 gm Infants. Am J Obstet Gynecol 1993;170:48-53.

Rouse DJ, Goldenberg RL, Cliver SP, et al. Strategies for the Prevention of Early Onset Neonatal Group B Streptococcal Sepsis: A Decision Analysis. Obstet Gynecol 1994;83:483-94.

Goldenberg RL, Cliver SP, Bronstein J, et al. Bed Rest in Pregnancy. Obstet Gynecol 1994;84:131-36.

Andrews WW, Hauth JC, Goldenberg RL, et al. Amniotic Fluid Interleukin-6: Correlation with Upper Genital Tract Microbial Colonization and Gestational Age in Women Delivered Following Spontaneous Labor versus Indicated Delivery. Am J Obstet Gynecol 1995:173(2):606-12.

Goldenberg RL, Tamura T, Neggers Y, et al. The Effect of Zinc Supplementation on Pregnancy Outcome. JAMA 1995;274:463-68.

Rouse DJ, Owen J, Goldenberg RL, et al. Zidovudine for the Prevention of Vertical HIV Transmission: A Decision Analytic Approach. J Acquired Immune Deficiency Syndrome 1995;9:401-07.

Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced Incidence of Preterm Delivery with Metronidazole and Erythromycin in Women with Bacterial Vaginosis. N Engl J Med 1995;333:1732-36.

Iams JD, Goldenberg RL, Meis PJ, et al. The Length of the Cervix and the Risk of Spontaneous Premature Delivery. N Engl J Med 1996;334(9):567-72.

Goldenberg RL, Mercer BM, Meis PJ, et al. The Preterm Prediction Study: Fetal Fibronectin Testing and Spontaneous Preterm Birth. Obstet Gynecol 1996;87:643-48.

Goldenberg RL, Iams JD, Mercer BM, et al. The Preterm Prediction Study: Fetal Fibronectin Bacterial Vaginosis and Peripartum Infection. Obstet Gynecol 1996;87:656-60.

Goldenberg RL, Klebanoff MA, Nugent R, et al. Bacterial Colonization of the Vagina During Pregnancy in Four Ethnic Groups. Am J Obstet Gynecol 1996;174:1618-21.

Goldenberg RL, Andrews WW. Editorial. Intrauterine Infection and Why Preterm Prevention Programs Have Failed. Am J Pub Health 1996;86:781-83.

Rouse DJ, Owen J, Goldenberg RL, et al. The Effectiveness and Costs of Elective Cesarean Delivery for Fetal Macrosomia Diagnosed by Ultrasound. JAMA 1996;276:1480-86.

Goldenberg RL, Cliver SP, Mulvihill FX, et al. Medical, Psychosocial and Behavioral Risk Factors Do Not Explain the Increased Risk for Low-Birth Weight in Black Women. Am J Obstet Gynecol 1996;175:1317-24.

Goldenberg RL, Tamura T, DuBard M, et al. Plasma Ferritin and Pregnancy Outcome. Am J Obstet Gynecol 1996;175:1356-59.

Goldenberg RL, DuBard MB, Cliver SP, et al. Pregnancy Outcome and Intelligence at Age Five Years. Am J Obstet Gynecol 1996;175:1511-15.

Goldenberg RL, Rouse DJ. Preterm Birth, Cerebral Palsy and Magnesium: Where Are We? Nature Medicine 1997;3:146-47.

Goldenberg RL, Andrews WW, Yuan A, et al. Sexually Transmitted Diseases and Adverse Outcomes of Pregnancy. Clin Perinatol 1997;24:23-41.

Goldenberg RL, Hickey CA, Cliver SP, et al. Abbreviated Scale for the Assessment of Psychosocial Status in Pregnancy: Development and Evaluation. ACTA Obstet Gynecol Scand 1997 (Suppl 165);76:19-29.

Goldenberg RL, Mercer BM, Iams JD, et al. The Preterm Prediction Study: Patterns of Cervicovaginal Fetal Fibronectin as Predictors of Spontaneous Preterm Delivery. Am J Obstet Gynecol 1997;177:8-12.

Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, et al. Antibiotic Therapy for the Reduction of Morbidity and Mortality After Preterm Premature Rupture of the Membranes. JAMA 1997;278:989-95.

Goldenberg RL, Cliver SP. Small for Gestational Age and Intrauterine Growth Restriction: Definitions and Standards. Clin Obstet Gynecol 1997;40:704-14.

Goldenberg RL, Iams JD, Mercer BM, et al. The Preterm Prediction Study: The Value of New versus Standard Risk Factors in Predicting Early and All Spontaneous Preterm Birth. Am J Public Health 1998;88:233-38.

Goldenberg RL, Andrews WW, Hauth JC. Markers of Preterm Birth. Prenat Neonat Med 1998;3:43-46.

Goldenberg RL, Rouse DJ. The Prevention of Premature Birth. N Engl J Med 1998;339:313-20.

Goldenberg RL, Hoffman HJ, Cliver SP. Neurodevelopmental Outcome of Small-For-Gestational-Age Infants. Eur J Clin Nutr 1998;52:S54-S58.

Tu FF, Goldenberg RL. Plasma Matrix Metalloproteinase-9 (MMP-9) Levels as Predictors of Spontaneous Preterm Birth. Obstet Gynecol 1998;92:446-49.

Goldenberg RL, Vermund SH, Goepfert A, et al. Choriodecidual Inflammation: A Potentially Preventable Cause of Perinatal HIV Transmission? The Lancet 1998;352:1927-30.

Klesges LM, Goldenberg RL, Cliver SP. Placental Calcification: Relationships with Cigarette Smoking and Dietary Antioxidants. Am J Epidemiology 1998;147:127-35.

Goldenberg RL, Mercer BM, Miodovnik M, et al. Plasma Ferritin, Premature Rupture of Membranes and Pregnancy Outcome. Am J Obstet Gynecol 1998;179:1599-604.

Leviton LC, Goldenberg RL, Baker CS, et al. Methods to Encourage the Use of Antenatal Corticosteroid Therapy for Fetal Maturation: A Randomized Controlled Trial. JAMA 1998;281:46-52.

Stringer JSA, Rouse DJ, Goldenberg RL. Prophylactic Cesarean for the Prevention of Perinatal HIV Transmission: The Case for Restraint. JAMA 1999;281:1946-49.

Pending Publication

Goldenberg RL, Andrews WW, Guerrant RL, et al. The Preterm Prediction Study: Lactoferrin, Other Markers of Vaginal Infection, and Preterm Birth. Am J Obstet Gynecol 2000;182:631-5.

Goldenberg RL, Andrews WW, Mercer BM, et al. Granulocyte Colony Stimulating Factor and Spontaneous Preterm Birth. Am J Obstet Gynecol 2000;182:625-30.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
John C. Hauth, M.D.	Interim Chairman, Professor and Director Center for Research in Women's Health

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(S)	FIELD OF STUDY
United States Air Force Academy, Colorado Springs, CO	B.S	1964	Engineering
University of Alabama at Birmingham, Birmingham, AL	M.D.	1968	Medicine

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

POST-GRADUATE TRAINING

Wildord Hall USAF Medical Center, Lackland AFB, TX, Residency in Obstetrics and Gynecology, 1968-1973
University of Texas Southwestern Medical School Dallas, TX, Fellowship in Maternal-Fetal Medicine, 1974-1976

FACULTY/ADMNISTRATIVE POSITIONS

Chief, Obstetrics and Gynecology Department, Hill AFB, UT, August 1973 to July 1974
Chief, Obstetrics Service, Wilford Hall USAF Medical Center, Lackland AFB, TX, November 1976 to June 1980
Military Consultant to the Air Force Surgeon General for Obstetrics and Gynecology, October 1980 to January 1987
Chairman and Residency Program Director, Department of Obstetrics and Gynecoogy, Wilford Hall USAF Medical Center, Lackland AFB, TX, July 1, 1980 to January 1987
Program Director, Materna-Fetal Medicine Fellowship, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, 1987 to 1993
Director of the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, January 1987 to September 30, 1997
Professor, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham, Birmingham, AL, January 1987 to present
Vice Chairman for Research, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, March 1998 to September 1999
Director, Center for Research in Women's Health, Department of Obstetrics and Gynecology, University of Alabama at Birmigham, Birmingham, AL, March 1998 to present
James Marion Sims Professor in Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, September 17, 1999 to present
Interim Chairman, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, October 1, 1999 to present

NATIONAL CONTRIBUTIONS

Chairman/Member, American College of Obstetricians and Gynecologists Committee on Obstetrics: Maternal and Fetal Medicine, 1985 to 1991
Member, National Institutes of Health National Institute of Child Health and Human Development Initial Review Group, Maternal and Child Health Research Subcommittee, 1996 to present
Consultant, National Institute of Dental Research, 1998 to present

PUBLICATIONS (Selected from 147 peer reviewed articles)

Hauth JC, Goldenberg RL, Parker CR Jr, Copper RL, Cutter GR. Maternal serum thromboxane B_2 reduction versus pregnancy outcome in a low-dose aspirin trial. Am J Obstet Gynecol 173:578-84, 1995.
Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. N Engl J Med 333:1732-6, 1995.
Hauth JC. Fetal monitoring: Utility and interpretation of umbilical cord blood gases and fetal scalp sampling. In: Wright LL, Merenstein GB, Hirtz D., ed. Report of the workshop on the definition of acute perinatal asphyxia in the term newborn. U.S. Department of Health and Human Services, National Institutes of Health, March 63-72, 1996.
Rouse DJ, **Hauth JC**, Andrews WW, Mills BB, Maher JE. Chlorhexidine vaginal irrigation for the prevention of peripartal infection: A placebo-controlled randomized clinical trial. Am J Obstet Gynecol 176:617-22, 1997

Levine RJ, **Hauth JC**, Curet LB, Sibai BM, Catalano PM, Morris CD, DerSimonian R, Esterlitz JR, Raymond EG, Bild DE, Clemens JD, Cutler JA. Trial of calcium to prevent preeclampsia. N Engl J Med 337:69-76, 1997.

Guinn DA, Goepfert AR, Owen J, Brumfield C, **Hauth JC**. Management options in women with preterm uterine contractions: A randomized clinical trial. Am J Obstet Gynecol 177:814-8;1997.

Goldenberg RL, Andrews WW, **Hauth JC**. Markers of preterm birth. Prenatal Neonatal Med 3:43-6, 1998.

Hauth JC, Andrews WW, Goldenberg RL. Infection-related risk factors predictive of spontaneous preterm labor and birth. Prenatal Neonatal Med 3:86-90, 1998.

Caritis S, Sibai B, **Hauth J**, Lindheimer MD, Klebanoff M, Thom E, VanDorsten P, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G, and the the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Low-dose aspirin to prevent preeclampsia in women at high risk. N Engl J Med 338:701-5, 1998.

Sibai BM, Lindheimer M, **Hauth J**, Caritis S, Klebanoff M, MacPherson C, VanDorsten P, Landon M, Paul R, Miodovnik M, Meis P, Dombrowski M, and the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Risk factors for preeclampsia, abruptio, and adverse neonatal outcomes in women with chronic hypertension. N Engl J Med 339:667-71, 1998.

Wenstrom KD, Andrews WW, **Hauth JC**, Goldenberg RL, DuBard MB, Cliver SP. Elevated second-trimester amniotic fluid interleukin-6 levels predict preterm delivery. Am J Obstet Gynecol 178:546-50, 1998.

Guinn DA, Goepfert AR, Owen J, Wenstrom KD, **Hauth JC**. Terbutaline pump for prevention of preterm delivery: A double-blind trial. Am J Obstet Gynecol 179:874-8,1998.

Kimberlin DF, Weller S, Whitley RJ, Andrews WW, **Hauth JC**, Lakeman F, Miller G. Pharmacokinetics of oral Valaciclovir and Acyclovir in late pregnancy. Am J Obstet Gynecol 179:846-51, 1998.

Caritis S, Sibai B, **Hauth JC**, Lindheimer M, VanDorsten P, Klebanoff M, Thom E, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G, Dombrowski M, McNellis D, and the NICHD Network of MFM Units. Predictors of pre-eclampsia in women at high risk. Am J Obstet Gynecol 179:946-51, 1998.

Hauth JC, Sibai B, Caritis S, VanDorsten P, Lindheimer M, Klebanoff M, MacPherson C, Landon M, Paul R, Miodovnik M, Meis P, Dombrowski M, Thurnau G, Walsh S, McNellis D, Roberts JM, and the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Maternal serum thromboxane B_2 concentrations do not predict improved outcomes in high risk pregnancies in a low-dose aspirin trial. Am J Obstet Gynecol 179:1193-9, 1998.

Wenstrom KD, Andrews WW, Bowles NE, Towbin JA, **Hauth JC**, Goldenberg RL. Intrauterine viral infection at the time of second trimester genetic amniocentesis. Obstet Gynecol 92:420-4, 1998.

Andrews WW, Tsao J, Goldenberg RL, **Hauth JC**, Mercer B, Iams J, Meis P, Moawad A, Das A, VanDorsten PJ, Caritis SN, Thurnau G, Miodovnik M, Roberts J, McNellis D. The Preterm Prediction Study: Failure of midtrimester cervical sialidase level elevation to predict subsequent spontaneous preterm birth. Am J Obstet Gynecol 180:1151-4, 1999.

Bottoms SF, Iams JD, Paul RH, Mercer BM, MacPherson CA, Roberts JM, Caritis SN, Moawad AH, VanDorsten JP, **Hauth JC**, Thurnau GR, Miodovnik M, Meis P, McNellis D for the NICHD Maternal Fetal Medicine Units Network. Obstetrical determinants of neonatal survival: Antenatal predictors of neonatal survival and morbidity in extremely low birth weight infants. Am J Obstet Gynecol 180:665-9, 1999.

Chapman SJ, **Hauth JC**, Bottoms SF, Iams JD, Sibai B, Thom E, Moawad AH, Thurnau GR. Benefits of maternal corticosteroid therapy in infants weighing ≥1000 gram at birth after preterm rupture of the amnion. Am J Obstet Gynecol 180:677-82, 1999.

Kimberlin DF, **Hauth JC**, Owen J, Bottoms SF, Iams JD, Mercer BM, Thom EA, Moawad AH, VanDorsten JP, Thurnau GR. Indicated versus spontaneous preterm delivery: An evaluation of neonatal morbidity among infants weighing ≤1000 grams at birth. Am J Obstet Gynecol 180:683-9, 1999.

Kimberlin DF, **Hauth JC**, Goldenberg RL, Bottoms SF, Iams JD, Mercer B, MacPherson C. The effect of maternal magnesium sulfate treatment on neonatal morbidity in ≤1,000 gram infants. Am J Perinatol 15:635-41, 1998.

Rouse DJ, Owen J, **Hauth JC**. Active-phase arrest: Oxytocin augmentation for at least 4 hours. Obstet Gynecol 93:323-8, 1999.

Goepfert AR, Goldenberg RL, **Hauth JC**, Bottoms SF, Iams JD, Mercer B, MacPherson CA, Moawad AH, VanDorsten JP, Thurnau GR. Obstetrical determinants of neonatal neurological morbidity in ≤1000 gram infants. Am J Perinatol 16:33-42, 1999.

Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, Catalano PM, Morris CD, for the Calcium for Preeclampsia Prevention Study Group. Pregnancy outcomes in healthy nulliparas who developed hypertension. Obstet Gynecol 95:24-8, 2000.

Sibai BM, Caritis S, **Hauth J**, Lindheimer M, VanDorsten JP, MacPherson C, Klebanoff M, Landon M, Miodovnik M, Paul R, Meis P, Dombrowski M, Thurnau G, Roberts J, McNellis D. Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. Am J Obstet Gynecol 182:364-9, 2000.

Andrews WW, Copper R, **Hauth JC**, Goldenberg RL, Neely C. Second-trimester cervical ultrasound: associations with increased risk for recurrent early spontaneous delivery. Obstet Gynecol 95:222-6, 2000.

Carey JC, Klebanoff MA, **Hauth JC**, Hillier SL, Thom EA, Ernest JM, Heine RP, Nugent RP, Fischer ML, Leveno KJ, Wapner R, Varner M. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. N Engl J Med 342:581-3, 2000.

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Kathleen G. Nelson, M.D.	Professor of Pediatrics, Associate Dean for Students

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
St. John's University	B.S.	1967	Biology
New York Medical College	M.D.	1971	Medicine
Children's hospital, Los Angeles	Intern	1972	Pediatrics
Yale New Haven Hospital	Resident	1974	Pediatrics
Yale University	Fellow	1976	Clinical Scholar

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE:

1995-Present	Associate Dean for Students
1989-Present	Professor, Pediatrics, Division of General Pediatrics, UAB
1984-1995	Director, Division of General Pediatrics, UAB
1982-Present	Associate Professor, School of Ed., UAB
1982-Present	Assistant Professor, School of Public Health, UAB
1982-1989	Associate Professor of Pediatrics, UAB
1976-1984	Assistant Director, Outpatient Services, The Children's Hospital
1976-1982	Assistant Professor of Pediatrics, Univ. of Alabama, Birmingham (UAB)
1975-1976	Medical Director, Community Health Center, Middle, CT
1973-1976	Attending Pediatrics, Fair Haven Community Health Center
1974-1976	Fellow, Robert Wood Johnson Clinical Scholars Program, Yale

SELECTED PEER REVIEWED PUBLICATIONS:

Goldenberg RL, **Nelson KG**, Koski JF, Cutter: Low birthweight, intrauterine growth retardation and preterm delivery. Am J Obstet Gynecol 152:980-983, 1985.

Goldenberg RL, Koski J, Ferguson C, Wayne J, Hale CB, **Nelson KG**. Infant mortality: relationship between neonatal and postneonatal mortality during a period of increasing perinatal center utilization. J Pediatr 106: 301-303, 1985.

Goldenberg RL, **Nelson KG**, Koski JF, Cutter G, Cassady GE. Neonatal mortality in infants born weighing 501-1000 grams. The influence of changes in birth weight distribution and birth weight-specific mortality rates on neonatal survival. Am J Obstet Gynecol 151:608-611, 1985.

Goldenberg RL, **Nelson KG**, Burton M, Anderson JH, Wayne JB. Gestational age and the management of preterm labor in obstetric programs. Am J Perinatol 2:25-29, 1985.

Goldenberg RL, Foster JM, Cutter GR, **Nelson KG**: Fetal deaths in Alabama, 1974-1983: a birth weight-specific analysis. Obstet Gynecol 70:831-835, 1987.

Waites KB, Rudd PT, Crouse DT, Canupp KC, **Nelson KG**, Ramsey C, Cassell GH. Chronic ureaplasma urelyticum and mycoplasma hominis infections of central nervous system in preterm infants (see comments) Lancet 1:17-21, 1988.

Goldenberg RL, Cutter GR, **Nelson KG**, Foster J. Effects of very low birth weights on fetal and neonatal mortality rates in Alabama. Public Health Rep 104:488-492, 1989.

Waites KB, Duffy LB, Crouse DT, Dworsky ME, Strange MJ, **Nelson KG**, Cassell GH. Mycoplasmal infections of cerebrospinal fluid in newborn infants from a community hospital population. Pediatr Infect Dis J 9:241-245, 1990.

Goldenberg RL, Cliver SP, Cutter GR, Hoffman HJ, Cassady G, Davis RO, **Nelson KG**: Black-white differences in newborn anthropometric measurements. Obstet Gynecol 78:782-788, 1991.

Goldenberg RL, Hoffman HJ, Cliver SP, Cutter GR, **Nelson KG**, Copper RL. The influence of previous low birth weight on birth weight, gestational age, and anthropometric measurements in the current pregnancy. Obstet Gynecol 79:276-280, 1992.

Gaudier FL, Goldenberg RL, **Nelson KG**, Peralta-Carcelen M, Johnson SE, DuBard MB, Roth TY: Acid-base status at birth and subsequent neurosensory impairment in surviving 500 to 1000 gm infants. Am J Obstet Gynecol 170:48-53, 1994.

Haywood JL, Goldenberg RL, Bronstein J, **Nelson KG**, Carlo WA: Comparison of perceived and actual rates of survival and freedom from handicap in premature infants. Am J Obstet Gynecol 171:432-439, 1994.

Gardner MO, Goldenberg RL, Gaudier FL, Dubard MB, **Nelson KG**, Hauth JC. Predicting low Apgar scores of infants weighing less than 1000 grams: the effect of corticosteroids. Obstet Gynecol 85:170-174, 1995.

Gardner MO, Goldenberg RL, Cliver SP, Tucker JM, **Nelson KG**, Cooper RL: The origin and outcome of preterm twin pregnancies. Obstet Gynecol 85:553-557, 1995.

Cliver SP, Goldenberg RL, Cutter GR, Hoffman HJ, Davis RO, **Nelson KG**: The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol 85:625-630, 1995.

Atkinson MW, Goldenberg RL, Gaudier FL, Cliver SP, **Nelson KG**, Merkatz IR, Hauth JC. Maternal corticosteroid and tocolytic treatment and morbidity and mortality in very low birth weight infants. Am J Obstet Gynecol 173:299-305, 1995.

Rouse DJ, Hauth JC, **Nelson KG**, Goldenberg RL: The feasibility of a randomized clinical perinatal trial: maternal magnesium sulfate for the prevention of cerebral palsy. Am J Obstet Gynecol 175:702-706, 1996.

Brumfield CG, **Nelson KG**, Stotser D, Yarbaugh D, Patterson P, Sprayberry NK: 24-hour mother-infant discharge with a follow-up home health visit: results in a selected Medicaid population. Obstet Gynecol 88:544-548, 1996.

Goldenberg RL, DuBard MB, Cliver SP, **Nelson KG**, Blankson K, Ramey SL, Herman A: Pregnancy outcome and intelligence at age five years. Am J Obstet Gynecol 175:1511-1515, 1996.

Gardner M, Bronstein J, Goldenberg RL, Haywood JL, Cliver SP, **Nelson KG**: Physician opinions of preterm infant outcome and their effect on antenatal corticosteroid use. J Perinatol 16:431-434, 1996.

Gaudier FL, Goldenberg RL, **Nelson KG**, Peralta-Carcelen M, DuBard MB, Hauth JC: Influence of acid-base status at birth and Apgar scores on survival in 500-1000 gm infants. Obstet Gynecol 175:180-185, 1996.

Pichichero ME, McLinn S, Aronovitz G, Fiddes R, Blumer J, **Nelson KG**, Dashefsky B: Cefprozil treatment of persistent and recurrent acute otitis media. Pediatr Infect Dis J 16:471-478, 1997.

Nelson KG, Goldenberg RL, Hoffman HJ, Cliver SP. Growth and development during the first year in a cohort of low income term-born American children. Acta Obstet Gynecol Scand: 165:76-87-92, 1997.

McMurry J, Williams E, Schwartz MD, Douglas J, Van Kirk J, Konrad TR, Gerrity M, Bigby JA, **Nelson KG**, Linzer M for the SGIM Career Satisfaction Study Group: "Physician job satisfaction: developing a model using qualitative data. J Gen Int Med 12:711-714, 1997.

Anderson HW, Gotlieb SJ, **Nelson KG**, Johnson SE. Home environment and cognitive abilities in infants born small-for gestational-age. Acta Obstetricia et Cynecol Scan 165:82-86, 1997.

Sweitzer RS, Lowry JF, Georgeson KE, **Nelson KG**, Johnson SE. Hearing loss associated with neonatal ECMO: a clinical investigation. Int J Pediatr Otorhinolaryngol 41:339-345, 1997.

Haywood JL, Morse SB, Goldenberg RL, Bronstein J, **Nelson KG**, Carlo WA: Estimation of outcome and restriction of interventions in neonates. Pediatrics 102:e20, 1998.

St John EB, **Nelson KG**, Cliver SP, Bishnoi RR, Goldenberg RL: Cost of neonatal care according to gestational age at birth and survival status. Am J Obstet Gynecol 182:170-175, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Philips, Joseph B., III	Professor of Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Washington and Lee University	B.S.	1971	Chemistry
University of North Carolina	M.D.	1975	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1975-1977, Resident in Pediatrics, Mount Sinai Hospital, New York, NY
1977-1978, Resident in Pediatrics, Duke University, Durham, NC
1978-1980, Fellow in Neonatal/Perinatal Medicine, University of Florida, Gainesville, FL
1980-1986, Assistant Professor of Pediatrics, University of Alabama at Birmingham, Birmingham, AL
1986-1999, Associate Professor of Pediatrics, University of Alabama at Birmingham, Birmingham, AL
1992-1993, Visiting Associate Professor of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA.
1999-present, Professor of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

PUBLICATIONS DURING THE PAST THREE YEARS

Lin, F.Y. C.; Clemens, J.D.; Azimi, P.H.; Regan, J.A.; Weisman, L.E.; Philips, J. B., III; Rhoads, G.G.; Clark, P.; Brenner, R.A.; and Ferrieri, P.: Capsular Polysaccharide Types of Group B Streptococcal Isolates from Neonates with Early-Onset Systemic Infection. J. Inf. Dis. 177:790-792, 1998.

Rouse, D.J.; Philips, J.B., III; Mott, C.W.; Ware, J.C.; and Lin, F.Y.: Antibiotic Susceptibility Profile of Vertically Acquired Group B. Streptococcus. Am. J. Obstet, Gynecol. 92:931-934, 1998.

Ambalavanan, N.; Mariani, G.; Philips, J.B., III: Role of Peptide Growth Factors in Cardiovascular Development. In: Fetal and Neonatal Physiology, Polin,R.A.; Fox, W.W. (eds), pp. 814-826, 1998. W. B. Saunders, Co., Philadelphia, PA.

Ambalavanan, N.; Bulger, A.; Philips, J.B., III: Hypoxia-Induced Release of Peptide Growth Factors from Neonatal Porcine Pulmonary Artery Smooth Muscle Cells. Biol. Neonate 76:311-319, 1999.

Ambalavanan, N.; Mariani, G.; Bulger, A.; Philips, J.B., III: The Role of Nitric Oxide in Regulating Neonatal Pulmonary Artery Smooth Muscle Cell Proliferation. Biol. Neonate 76:291-300, 1999.

Pending Publication

Pending Publication

Pending Publication

Pending Publication

Pending Publication

Pending Publication

Pending Publication

Pending Publication

REPRESENTATIVE EARLIER PUBLICATIONS

Li, J.X.; Gray, B.M.; Oliver, J.R.; Lu, C.Y.; and Philips, J.B., III: Delayed Thromboxane Synthesis Inhibition, But Not Cholinergic Blockade, Reverses Group B Streptococcus-Induced Pulmonary Hypertension. Dev. Pharmacol. Therapeutics. 19:40-49, 1992.

Philips, J.B. III; Li, J.X.; Gray, B.M.; Pritchard, D.G.; Oliver, J.R.: Role of Capsule in Pulmonary Hypertension Induced by Group B Streptococcus. Pediatr. Res. 31:386-390, 1992.

Li, J.X.; Gray, B.M.; Pritchard, D.G.; Oliver, J.R.; Grantham, K.D.; and Philips, J.B., III: Capsular Type-Specific Polysaccharide Partially Inhibits Group B Streptococcus-Induced Pulmonary Hypertension. Am. Rev. Respir. Dis. 148:152-157, 1993.

Li, J.X.; Oliver, J.R.; Lu, C.Y.; Grantham, K.D.; and Philips, J.B., III: Age-Related Differences in Responses to Endotoxin Infusion in Unanesthetized Piglets. Circ. Shock 41:40-47, 1993.

Horbar, J.D.; Wright, L.L.; Soll, R.F.; Wright, E. C.; Fanaroff, A.A.; Korones, S.B.; Shankaran, S.; Oh, W.; Fletcher, B.D.; Bauer, C.R.; Tyson, J.E.; Lemons, J.A.; Donovan, E.F.; Stoll, B.J.; Stevenson, D.D.; Papile, L.A.; and Philips, J., III: A Multicenter Randomized Trial Comparing Two Surfactants for the Treatment of Neonatal Respiratory Distress Syndrome. J. Pediatr. 123:757-766, 1993.

Berry, D.D.; Pramanik, A.K.; Philips, J.B., III; Butcher, D.S.; Kanarek, K.S.; Easa, D.; Edwards, K.; Long, W.; and the American Exosurf Neonatal Study Group II: Comparison of the Effect of Three Doses of a Synthetic Surfactant on the Alveolar-Arterial Oxygen Gradient in Infants Weighing > 1250 grams with Respiratory Distress Syndrome. J. Pediatr. 124:294-301, 1994..

Barefield, E.S.; Hicks, T.P.; Philips, J.B., III: Thromboxane and Pulmonary Morphometry in the Development of the Pulmonary Hypertensive Response to Group B Streptococcus. Crit. Care Med. 22:506-514, 1994.

Fanaroff, A.A.; Korones, S.; Wright, L.L.; Wright, E. C.; Poland, R.; Bauer, C.; Tyson, J.; Philips, J.B., III,; Edwards, W.; Lucey, J.; Shankaran, S.; and Oh, W.: A Controlled Trial of Intravenous Immune Globulin to Reduce Nosocomial Infections in Very-Low-Birth-Weight Infants. New Engl. J. Med. 330:1107-13, 1994.

Li, J.X.; Kelly, D.R.; Oliver, J.R.; and Philips, J.B. III: Effects of Cholinergic Blockade on Hemodynamic Disturbances and Intestinal Lesions in Endotoxic Shock in Newborn Piglets. Shock 2:98-105, 1994.

Li, J.X.; Oliver, J.R.; Lu, C.Y.; and Philips, J.B., III: Delayed Thromboxane or Tumor Necrosis Factor- alpha, but not Leukotriene Inhibition Attenuates Prolonged Pulmonary Hypertension in Endotoxemia. Am. J. Med. Sci. 310:103-110, 1995.

Li, J.X.; Oliver, J.R.; and Philips, J.B., III: Endotoxin Induces Biphasic Alterations in Small Intestinal Myoelectric Activity in Fasted Newborn Piglets. Pediatr. Res. 40:822-826, 1996.

Barefield, E.S.; Karle, V.S.; Philips, J.B., III; Carlo, W.A.: Inhaled Nitric Oxide in Term Infants With Hypoxemic Respiratory Failure. J Pediatr. 129:279-286, 1996.

Lott, J.D.; Conner, G.K.; Norton, J.; and Philips, J. B., III: Umbilical Artery Catheter Blood Sampling Alters Cerebral Blood Flow Velocity in Preterm Infants. J. Perinatol. 16:341-345, 1996.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Craig T. Ramey, Ph.D.	University Prof. Psychology/Maternal & Child Health/ Neurobiology; Director, Civitan Int'l Research Center

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEARS(s)	FIELD OF STUDY
West Virginia University	BA	1965	Psychology
West Virginia University	MA	1967	Psychology
West Virginia University	Ph.D.	1969	Developmental Psychology
University of California at Berkeley	Postdoc	1969	Developmental Psychology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: CONCLUDING with present position, list, in chronological order, previous employment, experience and honors. Include present membership of any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publication in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

PROFESSIONAL EXPERIENCE

1969-1971 Assistant Professor of Psychology, Wayne State University
1971-1978 Associate Professor, Department of Psychology, and Director of Infant Research, UNC Frank Porter Graham Child Development Center, at Chapel Hill
1975-1989 Director of Research, Frank Porter Graham Child Development Center, UNC at Chapel Hill
1979-1990 Professor of Psychology, UNC at Chapel Hill
1990-Present Director, Civitan International Research Center, University Professor of Psychology, Pediatrics, Maternal and Child Health, and Neurobiology, University of Alabama at Birmingham (UAB)

PUBLICATIONS

Blair, C., & Ramey, C.T. (1997). Early intervention for low birth weight infants and the path to second-generation res
Ramey, C. T., Sparling, J. J., Bryant, D. M., & Wasik, B. H. (1997). The intervention model. In R. T. Gross, D. Spiker, & C.W. Haynes (Eds.), Helping low birth weight premature babies: The Infant Health and Development Program (pp. 17-26). Stanford, CA: Stanford University Press.
Bryant, D. M., Ramey, C. T., Sparling, J. J., & Wasik, D. H. (1997). The child development centers. In R. T. Gross, D. Spiker, & C.W. Haynes (Eds.), Helping low birth weight premature babies: The Infant Health and Development Program (pp. 42-58). Stanford, CA: Stanford University Press.
Wasik, B.H., Bryant, D.M., Lyons, C., Sparling, J.J., & Ramey, C.T. (1997). Home visiting. In R.T. Gross, D. Spiker, & C. Hayes (Eds.), Helping low birth weight premature babies: The Infant Health and Development Program (pp. 27-41). Stanford, CA: Stanford University Press.
Ramey, C.T., Bryant, D., Wasik, B.H., Sparling, J.J., Fendt, K.H., & LaVange, L.M. (1997). Participation in intervention and its effects on cognitive outcome. In R.T. Gross, D. Spiker, & C. Haynes (Eds.), Helping low birth weight premature babies: The Infant Health and Development Program. 190-202. Stanford, Press.
Ramey, S.L., & Ramey, C.T. (1997). The role of universities in child development. In H.J. Walberg, R.P. Weissberg, & O. Reyes (Eds.), Children and youth: Interdisciplinary perspectives (pp. 13-44). Thousand Oaks, CA: Sage Publishing.
Burchinal, M.R., Campbell, F.A., Bryant, D.M., Wasik, B.H., & Ramey, C.T. (1997). Early intervention and mediating processes in cognitive performance of children of low-income African American families. Child Development, 68, 935-954.
Ramey, S.L., & Ramey, C.T. (1997). Evaluating educational programs: Strategies to understand and enhance educational effectiveness. In C. Seefeldt & A. Galper (Eds.), Continuing issues in early childhood education (2nd ed.) (pp. 274 - 292). Englewood Cliffs, NJ: Prentice.
Ramey, C.T., & Ramey S.L. (1997). The development of universities and children. Commissioned paper for the Harvard Project on Schooling and Children. Cambridge, MA: Harvard University Press.
Ramey, C.T., & Ramey, S.L. (1998). Prevention of intellectual disabilities: Early interventions to improve cognitive development. Preventive Medicine, 27, 224-232.
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Ramey, C.T., & Ramey, S.L. (1998). Early intervention and early experience. American Psychologist, 53, 109-120.
Ramey, S.L., Gaines, R., Phillips, M., & Ramey, C.T. (1998). Perspectives of former Head Start children and their parents on the transition to school. Elementary School Journal, 98, 311-328.

Ramey, C.T., Campbell, F.A., & Blair, C. (1998). Enhancing the life-course for high-risk children: Results from the Abecedarian Project. In J. Crane (Ed.), Social programs that really work (pp. 163-183). NY: Sage Publishing.

Ramey, S.L., & Ramey, C.T. (1998). The transition to school: Opportunities and challenges for children, families, educators, and communities. Elementary School Journal, 98, 293-296.

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Pending Publication

Lanzi, R.G., Washington, W.N., Ramey, S.L., Ramey, C.T., & Phillips, M.M. (1998). The transition to school experience: Myths, facts, and practical applications. NHSA Research Quarterly, 1, 160-180.

Pending Publication

Pending Publication

Pending Publication

Ramey, S. L., Ramey, C. T., & Friedlander, M. J. (Eds.). (1999). Mental Retardation and Developmental Disabilities Research Reviews. NY: John Wiley and Sons.

Ramey, S. L., & Ramey, C. T. (1999). Early experience and early intervention for children "at risk" for developmental delay and mental retardation. Mental Retardation and Developmental Disabilities Research Reviews, 5, 1-10.

Ramey, C. T., & Ramey, S. L. (1999). Right from birth: Building your child's foundation for life. New York: Goddard Press.

Pending Publication

Pending Publication

Pending Publication

REPRESENTATIVE EARLIER PUBLICATIONS

Moser, H. W., Ramey, C. T., & Leonard, C. O. (1990). Mental retardation. In A. E. H. Emery & D. L. Rimoin (Eds.), The principles and practices of medical genetics (Vol. II) (pp. 495-511). New York: Churchill Livingstone Inc.

Ramey, C. T., Bryant, D. M., Wasik, B. H., Sparling, J. J., Fendt, K. H., & LaVange, L. M. (1992). Infant Health and Development Program for low birth weight, premature infants: Program elements, family participation, and child intelligence. Pediatrics, 89, 454-465.

Ramey, C.T., & Ramey, S.L. (1994). Which children benefit the most from early intervention? Pediatrics, 94, 1064-1066.

Campbell, F.A., & Ramey, C.T. (1994). Effects of early intervention on intellectual and academic achievement: A follow-up study of children from low-income families. Child Development, 65, 684-698.

Ramey, S.L., & Ramey, C.T. (1994). The transition to school: Why the first few years matter for a lifetime. Phi Delta Kappan. 76, 194-198.

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program-director. Photocopy this page for each person.

NAME	POSITION TITLE
Dwight J. Rouse, M.D.	**Associate Professor, Obstetrics & Gynecology**

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Harvard College, Cambridge, MA	A.B.	1984	Biology
University of Illinois, Chicago, IL	M.D.	1988	
University of Iowa, Iowa City, IA	Certificate	1992	Internship & Residency/OB/GYN
University of Alabama at Birmingham Birmingham, AL	Certificate	1994	Fellowship, MFM

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

10/1/99 - Present: Associate Professor, OB/GYN, University of Alabama at Birmingham
4/10/97: Medical Director, UAB Obstetrics Complications Clinic
7/1/94 - 9/30/99: Assistant Professor, OB/GYN, University of Alabama at Birmingham

PUBLICATIONS:

Rouse DJ, Goldenberg RL, Cliver SP, Cutter GR, Mennemeyer ST, Fargason CA Jr. Strategies for the prevention of early onset neonatal group B Streptococcal sepsis: A decision analysis. Obstet Gynecol 1994;83:483-94.

Rouse DJ, Goldenberg RL, Cliver SP, Tamura T, Boots L: Mid-Trimester maternal serum alpha$_2$ macroglobulin and pregnancy outcome in a non-indigent population.Maternal-Fetal Med 1994;3:56-9.

Rouse DJ, Owen J, Goldenberg RL, Cliver SP. Determinants of the optimal time in gestation to initiate antenatal fetal testing: A decision-analytic approach. Am J Obstet Gynecol 1995;173:1357-63.

Rouse DJ, McCullough C, Wren AL, Owen J, Hauth JC. Active phase labor arrest: A randomized trial of chorioamnion management. Obstet and Gynecol 1994;83:937-40.

Rouse DJ, Owen J, Goldenberg RL, Vermund SH. Zidovudine for the prevention of vertical HIV transmission: A decision analytic approach. J Acquir Immun Def 1995;9:401-7.

Rouse DJ, Owen J, Goldenberg RL, Cliver SP. Determinants of the optimal time in gestation to initiate antenatal fetal testing? A decision-analytic approach. Am J Obstet Gynecol 1995;173:1357-63.

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Rouse, DJ. Asymptomatic Bacteriuria in Pregnancy. In: Wildschut JIJ, Weiner CP, Peters TJ, eds. When to Screen in Obstetrics and Gynecology. London:WB Saunders, 1996.

Rouse DJ, Hauth JC, Nelson KG, Goldenberg RL. Maternal Magnesium Sulfate for the Prevention of Cerebral Palsy: The Feasibility of a Randomized Clinical Trial. Am J Obstet Gynecol, 1996;175:701-6.

Rouse DJ, Gardner MO, Allen S, Goldenberg RL. Management of the presumed susceptible varicella (chickenpox)-exposed gravida: A decision analysis. Obstet Gynecol, 1996;87:932-6.

Alexander JM, Rouse DJ, Varner E, Austin JM. Treatment of the small unruptured ectopic pregnancy: A cost analysis of methotrexate versus laparoscopy. Obstet Gynecol 1996;88:123-7.

Rouse DJ, Hauth JC, Nelson KG, Goldenberg RL. Maternal magnesium sulfate for the prevention of cerebral palsy: The feasibility of a randomized clinical trial. Am J Obstet Gynecol 1996;175:701-6.

Gardner M, Rouse DJ, Goldenberg RL, Lanning J. Cost comparison of induction of labor at 41 weeks versus expectant management in the post-term pregnancy. Am J Man Care 1996;2:814-8.

Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. JAMA 1996;276:1480-6.

Rouse DJ, Hauth JC, Andrews WW, Mills BB., Maher JE. Chlorhexidine vaginal irrigation for the prevention of puerperal infection: A placebo-controlled randomized clinical trial. Am J Obstet Gynecol 1997;176:617-22.

Holley RL, Rouse DJ, Howard BC, Varner RE, Richter HE, Gleason BP. The cost-effectiveness of three surgical procedures for genuine stress incontinence. J Pelvic Surg 1997;3:246-50.

Fargason CA, Peralta-Carcelen M, Rouse DJ, Cutter GR, Goldenberg RL. The pediatric costs of strategies for minimizing the risk of early onset group B streptococcal disease. Obstet Gynecol 1997;90:347-52.

Rouse DJ, Goldenberg RL, Wenstrom KD. Antenatal screening for Factor V Leiden mutation: A critical appraisal. Obstet Gynecol,1997;90:848-50.

Munn MB, Rouse DJ, Owen J. Intraoperative hypothermia and post-cesarean wound infection. Obstet Gynecol 1998;91:582-4

Rouse DJ, Owen J, Goldenberg RL. Routine maternal platelet count: An assessment of a technologically-driven screening practice. Am J Obstet Gynecol 1998;179:573-6.

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Leviton LC, Goldenberg RL, Baker CS, Freda MC, Schwartz RM, Fish LJ, Cliver SP, Rouse DJ, et al. A randomized controlled trial of methods to encourage the use of antenatal corticosteroid therapy for fetal maturation. JAMA 1999:281:46-52.

Rouse DJ, Owen J, Hauth JC. Active phase labor arrest: Evaluation of a four-hour oxytocin minimum. Obstet Gynecol 1999;93:323-8.

Stringer JSA, Rouse DJ, Goldenberg RL. Prophylactic cesarean delivery for the prevention of vertical HIV transmission. The case for restraint. JAMA 1999;281:1946-49.

Stringer JSA, Rouse DJ. Rapid testing and zidovudine treatment to prevent vertical transmission of HIV in unregistered obstetrical patients: A cost-effectiveness and cost-benefit analysis. Obstet Gynecol, 1999;94:34-40.

Rouse DJ, Owen J. Prophylactic cesarean for fetal macrosomia diagnosed by ultrasound: A Faustian bargain? Am J Obstet Gynecol, 1999;181:332-8.

Stringer JSA, Rouse DJ, Goldenberg RL. Prophylactic cesarean delivery for the prevention of vertical HIV transmission. The case for restraint. JAMA, 1999;281:1946-49.

Pending Publication

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Robert L. Schelonka	Assistant Professor of Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Eastern New Mexico University, Portales, NM	1981	B.S	English and Education
Western Washington University, Bellingham, WA	1983	M.A.	Theater/Playwriting
Case Western Reserve, Cleveland, OH	1991	M.D.	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERENCE:

1991-1994 Pediatric Residency, Wilford Hall USAF Medical Center, San Antonio, TX
1994-1997 Fellowship in Neonatology, Wilford Hall USAF Medical Center, San Antonio, TX
1995-1997 Clinical Instructor, Department of Pediatrics, University of Texas Health Science Center, San Antonio, Texas
1997-2000 Neonatologist, United States Naval Hospital – Okinawa, Japan
2000-present Assistant Professor of Pediatrics, Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham

PUBLICATIONS

Schelonka RL, Yoder BA, Hall RB. White cell counting in newborns (Commentary). J Pediatr 1995;126:504-6.
Schelonka RL, Yoder BA, Hall RB, Trippett TM, Louder DS, Hickman JR, Guerra CG. Differentiation of segmented and band neutrophils during the early newborn period. J Pediatr 1995;127:298-300.
Schelonka RL, Yoder BA. The white cell count in newborns: It's uses and misuses. Contemporary Pediatr 1996;10:124-141.
Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DA. Volume of blood required to detect common neonatal pathogens. J Pediatr 1996;129:275-8.
Schelonka RL, Infante AJ. Neonatal immunology. Seminars in Perinatology 1998;22:2-24.
Schelonka RL, Raaphorst FM, Diane D, Ellen Kraig E, Teale JM, Infante AJ. T-cell receptor repertoire diversity and clonal expansion in human neonates. Pediatr Res 1998; 43:396-402.

Other Support

Name of Individual: Williams Andrews
Active/Pending: Active
Project Number (Principal Investigator): HD27869-U04 (John Hauth)
Source: National Institute of Child Health and Development
Title of Project (*and/or Subproject*): UAB Rural Perinatal Center: Infection and Prematurity
Dates of Approved/Proposed Project: 4/5/96-3/31/01
Direct Costs / Percent Effort: $470,272 % (Project 3) % (Project 4)

The major goals of this project are to determine if elevated amniotic fluid or umbilical cord blood cytokines are correlated with adverse neonatal outcomes; to determine if amniotic fluid or cord blood cytokines are correlated with specific laboratory and clinical findings that indicate possible neonatal sepsis. To evaluate infection related maternal risk factors and the prevention of preterm birth and infection related neonatal morbidity in rural Alabama women.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): P01 HD33927-02SI (John Hauth)
Source: National Institute of Health
Title of Project (*and/or Subproject*): UAB Rural Perinatal Center: Infection and Prematurity (Supplement)
Periodontal Disease and Preterm Birth
Dates of Approved/Proposed Project: 9/30/97-3/31/01
Direct Costs / Percent Effort: $187,959 %

The major goals of this project are to determine the association of periodontal disease with sexual and health behaviors and with preterm birth. To perform a prospective, randomized pilot intervention study of periodontal disease treatment to prevent preterm birth.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): HD 33883 (William Andrews)
Source: National Institute of Health
Title of Project (*and/or Subproject*): Interconceptional Antibiotics to Prevent Preterm Birth
Dates of Approved/Proposed Project: 9/20/96-8/31/00
Direct Costs / Percent Effort: $192,231 %

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): HD278-69 06 (William Andrews)
Source: National Institute of Child Health and Development
Title of Project (*and/or Subproject*): Cooperative Multicenter Network 1991-1996 Maternal-Fetal Medicine Units
Dates of Approved/Proposed Project: 5/1/91-3/31/01
Direct Costs / Percent Effort: $557,493 %

The major goal of this project is to accomplish obstetric clinical research trials such as low dose aspirin to prevent preeclampsia in low and high-risk women.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): NIAID1 PO1 AI43681-01 (Robert Pass)
Source: National Institute of Health
Title of Project (*and/or Subproject*): A Phase II/III Trial of Recombinant CMV gB Vaccine in Postpartum Women
Dates of Approved/Proposed Project: 7/1/98 -6/30/03
Direct Costs / Percent Effort: $264,277 %

The major goal of this project is to demonstrate an efficient means of evaluating the efficacy of a CMV vaccine, targeting postpartum women from a population with a demonstrated high rate of maternal and congenital CMV infection between pregnancies

Overlap (*summarized for each individual*): No scientific or budgetary overlap

% = Percentage of Effort

Active/Pending:	Active
Project Number (Principal Investigator):	NICHD-DESPR -97-08 (William Andrews)
Source:	National Institute of Child Health and Human Development
Title of Project (*and/or Subproject*):	Logitudinal Study of Vaginal Flora
Dates of Approved/Proposed Project:	5/1/98-3/31/02
Direct Costs / Percent Effort:	$2,347,633 %

The major goal of this project is to evaluate longitudinal changes in vaginal flora in non-pregnant women

Overlap (*summarized for each individual*): No scientific or budgetary overlap

% = Percentage of Effort

Other Support

Name of Individual: Waldemar A. Carlo
Active/Pending: Active
Project Number (Principal Investigator): HD34216-05 (Waldemar A. Carlo)
Source: National Institute of Child Health and Development
Title of Project (*and/or Subproject*): Multicenter Network of Neonatal Intensive Care Units
Dates of Approved/Proposed Project: 4/1/96 - 3/31/02
Annual Direct Costs / Percent Effort: $104,529 %

The major goals of this project are.to work with the NICHD and the Steering Committee to prioritize, plan, implement, analyze, interpret, and report a series of randomized and observational studies.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): 635026 (Waldemar A. Carlo)
Source: Alabama Department of Public Health
Title of Project (*and/or Subproject*): Perinatal Outreach Education Grant
Dates of Approved/Proposed Project: 10/1/99 - 9/30/00
Annual Direct Costs / Percent Effort: $97,850 %

The major goals of this project are.to enhance the education, practice, administration, and research for all health care providers in order to maintain and improve the health of infants and their families. The primary concern is to make appropriate learning opportunities available to nurses, doctors, and others in Perinatal Area III.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): (Waldemar A. Carlo)
Source: Private Support
Title of Project (*and/or Subproject*): Alabama Perinatal Care Conference
Dates of Approved/Proposed Project: 3/1/00-2/28/01
Annual Direct Costs / Percent Effort: $3,500

The major goals of this project are to provide for one of the special events of the conference agenda. First, a dual presentation on the subject of viability of the neonate. The second event is a Spanish language session designed to introduce conference participants to the wide range of translated educational materials and translation services available for perinatal patients. Didactic sessions for simple vocabulary and pronunciation will also be held to increase provider competence in using the language.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): (Waldemar A. Carlo)
Source: Private Support
Title of Project (*and/or Subproject*): Alabama Perinatal Care Conference
Dates of Approved/Proposed Project: 3/01/00-2/28/01
Annual Direct Costs / Percent Effort: $10,500

The major goals of this project are to provide two of the special events of the conference agenda. The first event is a seated dinner session that focuses on the Perspectives Panel on Viability, hosted by a prominent neonatologist and obstetrician from the State of Alabama. The second event is a continental breakfast session for the approximate 300 conference participants.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

✓

% = Percentage of Effort

Active/Pending: Active
Project Number (Principal Investigator): (Waldemar A. Carlo)
Source: Private Support
Title of Project (*and/or Subproject*): Alabama Perinatal Care Conference
Dates of Approved/Proposed Project: 3/01/00-2/28/01
Annual Direct Costs / Percent Effort: $25,500

The major goals of this project are to provide honorarium and travel expenses for the approximately 28 guest speakers at the Perinatal Outreach Education Conference. The conference brings together state health care leaders and major clinical centers across the United States to discuss the issues related to infant mortality, to hold problem solving workshops and to evaluate the programs sponsored by State funds. This three-day conference has statewide participation and seeks to bring together an expert panel of national recognized speakers on perinatal care.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): HD95-009 (William W. Andrews)
Source: National Institute of Health
Title of Project (*and/or Subproject*): UAB Rural Perinatal Center: Infection and prematurity. Project IV: Neonatal Systemic Inflammatory Response Syndrome: Role of Utero Cytokine Exposure
Dates of Approved/Proposed Project: 04/01/95-3/31/01
Annual Direct Costs / Percent Effort: $68,238 %

The major goals of this project are.to evaluate the relationship between in vetro exposure of the fetus to upper genital tract microoroganisms and/or proinflammatory cytokines in the amniotic fluid and clinically apparent sepsis-like syndrome that occurs in neonates within the first 48 hours of life.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): (Waldemar A. Carlo)
Source: Private Support
Title of Project (*and/or Subproject*): A comparative Study of the Use of the Aquaflo Hydrogel Dressing Versus Lansinoh Cream with Lactating Mothers
Dates of Approved/Proposed Project: 3/22/00-3/22/01
Annual Direct Costs / Percent Effort: $24,322 %

The major goals of this project are to evaluate the use of Aquaflo Hydrogel with lactating mothers and to compare this intervention to the standard treatment of hydrous lanolin cream.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): (Waldemar A. Carlo)
Source: Private Support
Title of Project (*and/or Subproject*): Inhaled NO in Neonates with Elevated A-a DO2 Gradients not Requiring Mechanical Ventilation
Dates of Approved/Proposed Project: 3/1/00-3/1/02
Annual Direct Costs / Percent Effort: $7,500 %

The major goals of this project are to evaluate whether administration of nitric oxide gas by oxygen hood at 20 ppm significantly increases PaO2, as compared to placebo gas (oxygen), within one-hour initiations, and with no significant adverse effects.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

% = Percentage of Effort

Active/Pending: Pending

Project Number (Principal Investigator):

Source: Pending Support

Title of Project (*and/or Subproject*):

Dates of Approved/Proposed Project:

Annual Direct Costs / Percent Effort:

Overlap (*summarized for each individual*): No scientific or budgetary overlap

GOLDENBERG, ROBERT L.

ACTIVE

Private Support (Goldenberg)	3/1/94 to 8/31/04	%
Smoke-Free Families	Annual Direct:	Total Direct:
To establish National Office and Grant Program for the Foundation to study smoking in pregnancy.	$1,100,917	$5,504,587
HD-95-009 (Hauth)	04/1/96 - 03/31/2001	%
NIH Perinatal Emphasis Research Center (PERC)	Annual Direct:	Total Direct:
UAB Rural Perinatal Center: Infection and Prematurity	$470,272	$2,280,851
To identify infection related maternal risk factors and attempt to prevent preterm birth and infection related neonatal morbidity in a rural population.		
AI97.77A (Vermund)	10/97 – 09/02	%
United States Agency for International Development	Annual Direct:	Total Direct:
(USAID)/The Population Council	$155,324	$723,416
HIV/AIDS Operations Research Project (HORIZONS)		
NO-HD-8-3293 (Andrews)	09/98 - 08/02	%
National Institute of Child Health and Human Development	Annual Direct:	Total Direct:
Longitudinal study of vaginal flora.	$540,360	$3,122,924
HIVNET 024 (Goldenberg)	10/98 - 03/02	%
The National Institute for Allergy and Infectious Diseases	Annual Direct:	Total Direct:
Phase III Trial of Antibiotics to Reduce Chorioamnionitis-Related Perinatal HIV Transmission	$264,223	$798,135
HD-99-001	07/99 – 06/04	%
National Institutes of Health	Annual Direct:	Total Direct:
OB-GYN Faculty Research Career Development Program	$370,223	$1,851,115
To assist junior faculty in develping research skills that can be applied to the study of important problems in women.		

OVERLAP

None

% = Percentage of Effort

HAUTH, J. C.

ACTIVE

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

2 U10 HD27869-06 (Hauth) 04/01/96 - 03/31/01 %
NIH-NICHD $739,379 Annual Direct $2,285,643 Total Direct
Cooperative Multicenter Network of 1991-2001 Maternal-Fetal Medicine Units

The major goal of this project is to accomplish obstetric clinical research trials such as low-dose aspirin to prevent preeclampsia in low and high risk women.

1 P01 HD33927-01 (Hauth) 05/01/96 - 04/30/01 %
NIH-NICHD $475,203 Annual Direct $2,279,775 Total Direct
UAB Rural Perinatal Center: Infection and Prematurity

The major goal of this project is to focus on rural maternal-infant health with a specific emphasis on infection related to preterm birth.

5 PO1 HD33927 (Hauth) 04/01/98 - 03/31/01 %
NIH-NIDR $168,883 Annual Direct $676,735 Total Direct
UAB Rural Perinatal Center: Infection and Prematurity (Supplement)

This supplement will study periodontal diseases as risk factors in preterm delivery.

1R01HD33883-01 (Andrews) 09/20/96 - 08/31/01 %
NIH-NICHD $185,332 Annual Direct $758,118 Total Direct
Interconceptional Antibiotics to Prevent Preterm Birth

The major goal of this project is to determine the effectiveness of interconceptional antibiotics in women who have had a previous preterm birth to prevent preterm birth in subsequent pregnancies.

NICHD-NO-HD-8-3293 (Andrews) 09/30/98 - 09/29/02 %
NIH-NICHD $540,360 Annual Direct $3,122,924 Total Direct
Longitudinal Study of Vaginal Flora

The major goal of this project is to determine the prevalence and incidence of bacterial vaginosis in a defined population of 5,000 initially nonpregnant women.

#1R01HD35914-01A1 (Rouse) 01/01/99 - 12/31/01 %
DHHS $113,917 Annual Direct $396,893 Total Direct
Chlorhexidine Irrigation for the Prevention
of Peripartal Infection

To determine whether treatment (vaginal irrigation) with dilute chlorhexidine solution will prevent or lessen maternal peripartal infections.

HD-99-001 (Hauth) 07/01/99 - 06/30/04 %
NIH-NICHD $370,223 Annual Direct $1,851,115 Total Direct
OB/GYN Faculty Research Career Development Program

The major goal of this project is to promote the performance of research and transfer of findings that will benefit the health of women by supporting the research career development of recently completed postgraduate trained obstetrician-gynecologists.

% = Percentage of Effort

PENDING

Pending Support

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Other Support

Name of Individual: Kathleen G. Nelson
Active/Pending: Active
Project Number (Principal Investigator): Kathleen G. Nelson
Source: Private Support
Title of Project (*and/or Subproject*): Minority Medical Education Program
Dates of Approved/Proposed Project: 2000-2005
Annual Direct Costs / Percent Effort: %

The major goals of this project are to identify promising minority students who are interested in medical careers and give them additional educational and practical experiences to improve their competitiveness in medical school application process.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): 523929 (Wally Carlo)
Source: National Institute of Health and Child Development
Title of Project (*and/or Subproject*): Cooperative Multicenter Neonatal Research Network
Dates of Approved/Proposed Project: 1995-2001
Annual Direct Costs / Percent Effort: $104,529

The major goals of this project are to work with the NICHD and the Steering Committee to prioritize, plan, implement, analyze, interpret, and report a series of randomized and observational studies and resolve current controversies in neonatal care.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): Co-Director (Kathleen Nelson)
Source: National Institute of Child Health and Human Development, Maternal Fetal Medicine Units Network, and the National Institute of Neurological Disorders and Stroke
Title of Project (*and/or Subproject*): Randomized Clinical Trials of the Beneficial Effects of Antenatal Magnesium Sulfate
Dates of Approved/Proposed Project: 1997-2002
Annual Direct Costs / Percent Effort: $2,000,000

The major goal of this project is to determine if antenatal magnesium sulfate will improve both short and long-term outcome for the neonate.

Overlap (*summarized for each individual*): No Scientific or budgetary overlap

Active/Pending: Active
Project Number (Principal Investigator): (Kathleen Nelson)
Source: State of Alabama Department of Education
Title of Project (*and/or Subproject*): Newborn Intensive Care Follow Up Program
Dates of Approved/Proposed Project: 1999-2000
Annual Direct Costs / Percent Effort: $69,195

The major goal of this project is to evaluate outcomes of children with prolonged NICU hospitalization including birthweight <1000 grams or post ECMO.

Overlap (*summarized for each individual*): No Scientific or budgetary overlap

% = Percentage of Effort

Other Support

Name of Individual:	Joseph B. Philips, III, M.D.
Active/Pending	Active
Project Number (Principal Investigator):	HD37227-01A1 (Joseph B Philips)
Source:	National Institute of Child Health and Human Development
Title of Project (*and/or Subproject*):	IGG Receptor Isoforms and Neonatal Infections
Dates of Approved/Proposed Project:	8/10/99-7/31/01
Annual Direct Costs / Percent Effort:	$100,000

The major goals of this project are...to determine whether low-responding genotypes of FcyRIIA, FcyRIIIA, and/or FcyRIIIB are over-represented in infants with hospital-acquired infections.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending	Active
Project Number (Principal Investigator):	1-R01-HD36292 (Harry Schroeder)
Source:	National Institute of Child Health and Human Development
Title of Project (*and/or Subproject*):	Ontogeny of the Perinatal Antibody Response
Dates of Approved/Proposed Project:	9/30/97-7/31/02
Annual Direct Costs / Percent Effort:	$141,500

The major goals of this project are...to elucidate the mechanisms that restrict the diversity of the perinatal antibody repertoire and to gain insight into the role these mechanisms play in limiting the response of the infant to infection and vaccination.

Overlap (*summarized for each individual*): No scientific or budgetary overlap

Active/Pending:	Pending (Joseph B Philips)
Project Number (Principal Investigator):	
Source:	Pending Support
Title of Project (*and/or Subproject*):	
Dates of Approved/Proposed Project:	
Annual Direct Costs / Percent Effort:	

Overlap (*summarized for each individual*): No scientific or budgetary overlap

OTHER SUPPORT

ACTIVE

105-95-1932 (C. Ramey) 09/30/95 - 01/31/00 %
ACYF $783,559
Comprehensive Child Development Program (CCDP) Longitudinal Follow-up Study (Cohort 1)

The primary purpose of the proposed follow-up study is to continue to assess, over an additional period of five years, the longitudinal impact of the Comprehensive Child Development Programs originally funded by the Administration on Children, Youth and Families (ACYF) in fiscal year (FY) 1989. In particular, the follow-up study will focus on studying families within a selected subset of 8 Cohort 1 CCDP sites. It is anticipated that the study will include, at minimum, two follow-up data collection points that will (1) enable the continued longitudinal examination of the CCDP intervention (comparing the outcomes for families who originally were randomly assigned to either the program or comparison groups), as well as (2) conducting an assessment of post-CCDP experiences and the tracking of developmental progress for both groups of children and families as the children move into and through preschool (including Head Start for some children) and the early elementary school grades.

P50-HD32901-02 (S. Ramey) 09/30/94 - 03/31/00 %
NICHD $739,911
Developmental Disabilities Prevention Research Center

This Center was established within a University Affiliated Program (UAP) to investigate critical problems of prevention and amelioration of developmental disabilities with a primary focus on myelin, CNS functional integrity, and critical influences on maturation, health, and human competency (especially the role of nutrition and its interactions with other pre- and postnatal environmental factors). The objectives of the Center are: (1) to conduct research to advance knowledge about the etiology, prevention, and treatment of developmental disabilities; (2) to enhance the research environment by providing high quality core support services; (3) to strengthen programmatic, multidisciplinary inquiry about myelinogenesis, CNS development, and developmental disabilities; (4) to foster new collaborations in promising areas and to recruit new investigators to the field, and (5) to promote timely dissemination of scientific discoveries.

105-95-1935 (S. Ramey) 09/30/95 - 06/30/00 %
ACYF $1,974,292 $4,338,026
National Head Start/Public School Early Childhood Transition Demonstration Project

Plan, oversee, and analyze the effect of a new, expanded Head Start Public School Early Childhood Transition program (from kindergarten to 3rd grade) on 12,000 children and families in 32 sites across the U.S. The study involves random assignment of schools to intervention or comparison groups. This congressionally mandated national study focuses on outcomes at the child, family, school, service delivery, and community levels.

04DD000162 (S. Ramey) 07/01/97 - 06/30/02 %
ADD $200,000
University Affiliated Program Core Grant

The Alabama UAP seeks: (1) to further strengthen the interdisciplinary training core program by including more direct training experiences related to cultural diversity -- in both urban and rural settings; (2) to expand the exemplary services and programs that are community-based, particularly those that respond to Alabama's most pressing needs (including early intervention and prevention, family and individual supports, assistive technology, the transition to adulthood and employment, aging, and assistance to rural families); (3) to provide technical assistance to service providers and direct care personnel, administrators, agencies, and organizations regarding developmental disabilities, especially concerning effective ways to meet the needs of previously underserved and unserved populations; and to increase the information dissemination and applied research activities that will improve the well-being and quality of life for individuals and families affected by developmental disabilities.

% = Percentage of Effort

HRSA MCJ-370632-01 (F. Campbell) 06/01/96 - 05/31/00 %
DHHS, MCHB $192,067 $768,000
Role of Early Family Supports in Adult Self-Sufficiency

The proposed study addresses the long-term, multigenerational outcomes of the Abecedarian project, a randomized clinical trial of early childhood educational intervention. This research represents the endpoint of a 21-year longitudinal study that began in the early infancy of the participants. Data collected at this point, informed by an extensive longitudinal database, contain important answers concerning ecological, personal, and situational factors associated with different developmental trajectories.

730 (C. Maddox) 07/01/97 - 06/30/01 %
Center for Disease Control and Prevention $349,571 $1,791,080
Alabama State Capacity Project

This project will redirect the current surveillance effort targeted at mental retardation, head and spinal cord injury, and secondary conditions into an expanded population-based statewide surveillance system of individuals affected by a disability in the learning domain, and will emphasize data collection focusing on secondary conditions and general health status. Secondary condition prevention and health promotion activities will be developed for this target population.

RO4/CCR414133-01 (J. Wallander) 08/01/97 - 07/31/00 %
Centers for Disease Control and Prevention $284,562 $834,800
Secondary Conditions in Youth with Mobility Disability

This project is a population-based study designed to develop a better understanding of the secondary conditions that occur among youth with a disability in the mobility domain and to inform efforts to improve their quality of life.

% = Percentage of Effort

Dwight J. Rouse, M.D.

OTHER SUPPORT

ACTIVE

1. RFA -90-HD-04 (Hauth) 4 / 96 -- 3 / 2001 %
NIH/NIC Annual Direct – $739,379 Total Direct – $2,285,643
A multicenter study--Cooperative Agreement Application Multicenter Network of Maternal-Fetal Medicine Units (MFMUs)

To conduct large scale clinical perinatal trials.

2. RO1HD35914-01A1 (Rouse) 1/99 – 12/01 %
DHHS Annual Direct -- $113,917 Total Direct – $556,645
Chlorhexidine Irrigation for the prevention of peripartal infection.

To determine whether treatment (vaginal irrigation) with dilute chlorhexidine solution will prevent or lessen maternal peripartal infections.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

% = Percentage of Effort

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory: A 100 sq. ft. laboratory is located within the regional NICU and contains a freezer, refrigerator, and other equipment as needed for clinical studies.

Clinical: The Regional NICU would serve as the performance site for Neonatal Network research activities. The 62-bed 10,000 sq. ft. unit receives inborn and outborn neonates from throughout Alabama, and selected infants from neighboring states.

Animal: Not Applicable

Computer: A dedicated computer was provided by the NICHD Neonatal Research Network through our past participation in the Network. The Division of Neonatology has multiple other IBM and McIntosh computer systems.

Office: Faculty and support personnel are officed in space adjacent to the Regional NICU.

Other: E-mail (Internet), facsimile machine, scanning capabilities, and Medline are available directly in the Division's office.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

The Division research laboratories, equipped for *in vitro* and *in vivo* physiological, cellular, and molecular research, are available for the Network research.

A full service biomedical engineering department and other support services are available at University Hospital and UAB. See Section 5. Facilities and Clinical Capabilities for other information,

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

☐ NEW application. *(This application is being submitted to the PHS for the first time.)*

☐ REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

☒ COMPETING CONTINUATION of grant number: 1V10HD34216
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl.only)*
☐ No ☐ Previously reported
☐ Yes. If "Yes," ☐ Not previously reported

☐ SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

☐ CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

☐ FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

•Human Subjects; •Vertebrate Animals; •Debarment and Suspension; •Drug-Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only);* •Lobbying; •Delinquent Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 19.)*

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

3. FACILITIES AND ADMINISTRATION COSTS (F & A)

Indicate the applicant organization's most recent F & A cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative F & A cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates,* and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. F & A costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, and specialized grant applications.

☒ DHHS Agreement dated: 5/19/99 ☐ No Facilities and Administration Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on F & A costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base $ 108,568 x Rate applied 43.5 % = F & A costs (1) $ 47,227

b. Entire proposed project period: Amount of base $ 572,448 x Rate applied 43.5 % = F & A costs (2) $ 249.015
(1) Add to total direct costs from form page 4 and enter new total on Face Page, Item 7b.
(2) Add to total direct costs from form page 5 and enter new total on Face Page, Item 8b.

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*
☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. SMOKE-FREE WORKPLACE

Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?
☐ Yes ☐ No *(The response to this question has no impact on the review or funding of this application.)*

Reprographic Communications Branch

Problem Notification

The Print Shops have been instructed by CSR Project Control that as long as the first 10 pages are present to duplicate grant application packages "as is" even if the application is not numbered consecutively or if pages in the application are missing.

While running this job, the Print Shop noted the following problems with this application package.

Bad originals resulting in poor copy quality _____

Pages _____ **through** _____ **missing.**

(These pages were missing from the original copy provided the Print Shop.)

Description of other problems:

49 and 74 missing

For further information, please contact: **Rockledge Job Planning on 435-0460 or Stonestreet Job Planning on 496-4808.**

1. ACADEMIC PRODUCTIVITY

The Division of Neonatology in the Department of Pediatrics at the University of Alabama at Birmingham (UAB) and the Regional Neonatal Intensive Care Unit (NICU) at UAB have been heavily involved in clinical research since their inception. From major multicenter industry- and federally-funded trials to single site trials supported by intramural or extramural funds, the Division has performed clinical research in a variety of disciplines. During the last decade, ten multicenter and six single center randomized clinical trials have been performed by members of the Division of Neonatology in the Regional NICU at UAB, in addition to the NICHD Neonatal Network studies. The number of patients enrolled into each of the randomized controlled trials (Section 1.1) and in five federally-funded observational Studies (Section 1.2) is summarized in Section 1.3. UAB has had a very active participation in the Neonatal Network, with three approved studies of the current 5-year cycle developed by this center. The detailed information in Sections 1.4, 1.5, and 1.6 documents that UAB has been a leading recruiter in all Network trials and studies. The principal investigator at UAB is chairperson of three protocol subcommittees (Minimal Ventilation, Cytokines, Sedation) and a member of the Generic Data Base, Neonatal-MFM Network Joint Liaison, Massage, Benchmarking, and Cord Clamping subcommittees. The strong record of multicenter and single center clinical trials and many contributions to the Network document this center's commitment to excellence in clinical research and ability to design and collaborate in clinical trials.

1.1. Recent and Current Clinical Trials - 1990 to 2000

In addition to UAB's participation in NICHD Neonatal Intensive Care Network, the Regional NICU has been the site of numerous clinical trials performed by members of the Division of Neonatology (single center) or in collaboration with other investigators (multicenter), highlighting UAB's innovative or collaborative role in clinical trials. Because priority is given to Network research, these trials have not interfered with Network patient enrollment.

1.1.1. Randomized Controlled Trials of Surfactants - 1990 to 1993 – Multicenter (5 trials)

UAB participated in four multicenter trials of Exosurf and one multicenter treatment trial of Infasurf - Survanta. At UAB the number of enrolled patients consistently exceeded expectations in each of the five trials. Despite an agreed estimated enrollment of 100 patients, UAB enrolled 107 patients in only 12 months (Bloom et al. 1997).

1.1.2. Randomized Trial of Feeding Advancements - 1994 to 1996 – Single Center (1 trial)

Prospectively collected observational data by the NICHD Neonatal Network revealed an increased incidence of necrotizing enterocolitis (NEC) in centers with rapid increments in feeding (Uauy et al. 1991). The Regional NICU at UAB was one of the two clinical centers that used rapid increases in feeding and had a high incidence of NEC. Thus, a single center randomized controlled pilot study was conducted at UAB to determine whether the rate of feeding advancement in formula-fed infants affects the incidence and/or severity of NEC (Rayyis et al. 1999, Appendix 1). Because the incidence of NEC is low in human milk-fed infants, 185 formula-fed infants with birth weight 501 to 1500 g were randomized to receive "slow" (15 cc/kg/day) or "fast" (35 cc/kg/day) feeding advances. The incidence of NEC (Bell stage $\geq$ II) was similar in both groups (slow 13% and fast 9%, $P = 0.5$). The incidence of perforation (Bell stage III) was also similar in both groups (slow 4% and fast 2%, $P = 0.8$). The neonates in the fast group attained full enteral intake earlier (median days [25th and 75th percentiles]: slow 15 [12, 21] and fast 11 [8, 15], $P < 0.001$) and regained their birth weight earlier (slow 15 [11, 20] and fast 12 [8, 15], $P < 0.05$). Thus, a greater than two-fold increase in the rate of feed advancement from 15 cc/kg/day to 35 cc/kg/day did not increase the incidence of NEC $\geq$ stage II and resulted in better nutrition.

1.1.3. Nitric Oxide Pilot Study and Multicenter Trial - 1993 to 1996 – Single Center (1 trial) and Multicenter (1 trial)

A March of Dimes-funded pilot study of inhaled nitric oxide was conducted in infants with pulmonary hypertension (Barefield et al. 1996). UAB was subsequently instrumental in the development of a national study, and Dr. Barefield St. John became a member of the four-person steering committee that directed and oversaw all aspects of the implementation of the protocol and data analysis of a multicenter trial. This study revealed that inhaled nitric oxide resulted in acute and sustained improvements in oxygenation that tend to reduce the need for ECMO (Davidson et al. 1998). The center at UAB enrolled more patients than expected.

1.1.4. Prevention of Respiratory Syncytial Virus (RSV) Trials - 1994 to 1996 – Multicenter (2 trials)

The Division participated in the original randomized trials of RespiGam™ (RSVIG-IV) and Synagis (palivizumab) for the reduction in respiratory syncytial virus hospitalizations in premature infants and in infants with bronchopulmonary dysplasia (The PREVENT Study Group 1997; The IMpact-RSV Study Group, 1998). It was challenging to maintain appointment compliance as these studies required monthly outpatient infusions or intramuscular injections, respectively, for up to five months. At UAB, all but one patient of 15 patients completed all aspects of the studies. Patients were seen in the outpatient clinics by the Division's neonatologists and research nurses.

1.1.5. Recombinant Human Superoxide Dismutase (rhSOD) Trials - 1994 to 1996 - Multicenter (2 trials)

The Division was one of six sites in the multicenter phase I multiple dose, placebo-controlled Safety and Tolerance of rhSOD Study in Premature Neonates with Respiratory Distress Syndrome (Davis et al. 1997) and the phase III Randomized Controlled Trial of rhSOD (Davis et al. 1999). Study personnel were on call 24 hours a day to enroll patients, assure protocol adherence, and perform laboratory studies. The Division's performance in both enrollment and follow-up was excellent.

1.1.6. Pilot Study of Permissive Hypercapnia in Infants 601 to 1250 g - 1995 to 1996 - Single Center (1 trial)

The purpose of this study was to determine whether a ventilatory strategy of permissive hypercapnia reduces the duration of assisted ventilation in surfactant-treated neonates weighing 601 to 1250 g at birth (Mariani et al. 1999, Appendix 1). Forty-nine surfactant-treated preterm infants (birth weight: 854 ± 163 g; gestational age: 26 ± 1.4 weeks) receiving assisted ventilation were randomized during the first 24 hours after birth to a permissive hypercapnia group ($PaCO_2$: 45-55 mm Hg) or to a

normocapnia group ($PaCO_2$: 35-45 mm Hg). The number of patients on assisted ventilation was reduced during the intervention period ($P < 0.005$, log rank test). The total number of days on assisted ventilation expressed as median (25^{th}-75^{th} percentiles) was 2.5 (1.5-11.5) in the permissive hypercapnia group and 9.5 (2.0-22.5) in the normocapnia group (NS). During the intervention period, the ventilated patients in the permissive hypercapnia group had a lower peak inspiratory pressure, mean airway pressure, and ventilator rate than those in the normocapnia group. This pilot study demonstrated the ability of the clinicians at UAB to conduct this type of ventilatory management trial in critically ill neonates.

1.1.7. Vitamin A Pharmacokinetics Pilot Study - 1999 to Current - Single Center (1 trial)

Following the results of the Neonatal Network randomized trial of vitamin A for the prevention of chronic lung disease (Tyson et al. 1999), vitamin A treatment was initiated at UAB in the infants with birth weight $\leq$ 1000 g receiving oxygen or ventilation at 24 hours after birth. However, because the Network study reported 25% of the infants in the supplemental group were still vitamin A deficient after treatment was completed, an ongoing randomized controlled study at UAB was designed to test three different vitamin A dosages to determine if a higher dose of vitamin A can reduce the proportion of infants with low retinol levels and if fewer but larger doses are safe. Forty-two patients of a planned study of 90 have been enrolled.

1.1.8. Pilot Study of Physiological Effects and Feasibility of Inhaled Nitric Oxide in Neonates with Elevated A-a DO_2 Gradient Not Requiring Mechanical Ventilation - 1999 to Current - Single Center (1 trial)

This is a randomized controlled pilot study to evaluate whether administration of nitric oxide gas by hood at 20 ppm increases PaO_2 as compared to placebo gas (oxygen) within one hour of initiation and prevents intubation in neonates with hypoxemic respiratory failure.

1.1.9. Trial of Gentle Touch/Massage on Preterm Infants - 1999 to Current - Single Center (1 trial)

This is a pilot study on the effects of gentle touch/massage on preterm infants performed by Lynda Harrison, R.N., Ph.D., in the Regional NICU in collaboration with Dr Carlo. Preterm infants (27 0/7 to 30 6/7 weeks gestation) are enrolled at 6-9 days of age and are randomized to receive either no intervention or 4 weeks of an intervention consisting of gentle touch and massage for 10 minutes per day. The interventions are being done behind a screen by a single trained research nurse to keep the rest of the investigators and care takers masked to the treatment group. Data are being recorded pre- and post-intervention to determine alterations in infant behavior and to determine the feasibility of a larger study. A grant from the National Institute of Nursing funded from an earlier study and another application is in preparation.

1.2. Recent and Current Observational Studies - 1993 to 2000

The Division of Neonatology at UAB has participated and provided leadership in many observational studies. Only federally-funded studies are listed.

1.2.1. Seizures in Very Low Birthweight Infants Study - 1993 to 1998

The Seizure in Very Low Birthweight Infants Study was a major observational study in the Regional NICU. This National Institute of Neurological Disorders-funded study was a prospective case-controlled study of infants with birthweight 501-1500 g that compared neonates who experienced either clinical or electroencephalographic seizures (cases) to a group of infants without either type of seizures. The purpose of the study was to characterize seizures in this population, determine the risk factors for seizures, assess the influence of brain maturation on seizure manifestation, and determine the effect of seizures on outcome. A unique aspect of this study was the performance of bedside video/electroencephalogram (EEG)/polygraphic monitoring in the Regional NICU on a 24-hour per day, seven-day per week basis. Seizure surveillance was performed by the NICU nurses (all staff nurses were trained on seizure recognition using specially developed teaching videotapes and post-tests for assessment of seizure identification skills). Dr. Carlo provided the neonatal expertise in this study and the center's principal investigator, Merrill Wise, M.D., conducted the study. All infants (cases and controls) received serial neurodevelopmental assessments after discharge at 6, 12, and 24 months of age in the Neonatal Intensive Care Follow-up Program. This study concluded that clinical seizures with normal EEG are the predominant seizure type in very low birthweight infants. It also demonstrated the ability of the NICU nursing staff to participate in the round-the-clock screening of patients for a clinical study (Wise et al. 1999).

1.2.2. Maternal Antibodies Against Group B Streptococcus in Neonates - 1994 to 1999

The multicenter NICHD study Determination of Protective Levels of Maternal Antibody Against Early-Onset Invasive Group B Streptococcal Disease in Neonates has been completed. The primary purpose of this study was to collect maternal and cord sera to determine protective levels of type-specific antibody by comparing sera from infants with early onset disease with those from colonized and non-colonized neonates. Geographical differences in the serotypes have been reported (Lin et al. 1998). Other data are being analyzed and prepared for publication.

1.2.3. Cytomegalovirus Infection Epidemiological Hearing Studies - 1995 to Current

Due to the high incidence of cytomegalovirus (CMV) infection in Alabama (twice the national rate), this ongoing observational study requires all infants to be screened for CMV. Positive infants and controls receive hearing tests soon after birth and throughout infancy as part of an NICHD-funded study on the epidemiology of hearing deficits in CMV positive infants.

1.2.4. Neonatal Sepsis-like Syndrome Related to *In Utero* Cytokine Exposure - 1996 to 1999

This NICHD-funded study aims to determine if inflammatory mediators at birth are associated with increased incidence of culture negative early neonatal sepsis. Diagnosis of early neonatal sepsis is based on a combination of historical, physical, and laboratory findings.

1.2.5. Ontogeny of the Perinatal Antibody Repertoire - 1997 to 1999

This NIAID-funded study assessed the cross-sectional and longitudinal development of the IgM, IgD, IgG, and IgA HCDR3 repertoires in fetal and preterm infants to determine the effect of infections and maternal IgG on the diversification of the repertoire as assessed by the distribution of HCDR3 lengths. Data are currently being analyzed and compiled.

1.2.6. The Role of IgG Receptor Isoforms in Neonatal Infection - 2000 to Current

Funded by NICHD, this study lead by J. Philips, M.D. (PI) is evaluating the role of genetic variability of IgG receptors in infants with late-onset sepsis. Infected infants will be compared to infants that do not have an infection during the time of hospitalization.

1.3. Enrollment for Recent and Current Clinical Trials and Observational Studies

Enrollment in recent and current clinical trials and observational studies is summarized in Table 1a. Data are stratified by race and gender to show adequate representation of minority infants and both genders in these studies. These proportions are comparable to that of infants admitted to the Regional NICU.

Table 1a. Gender and Race of Neonates Enrolled in Recent and Current Non-Network Clinical Trials

		GENDER		RACE		
RANDOMIZED TRIALS	Total	Male	Female	Black	White	Others
*Exosurf (Protocol 12)	11	10	1	6	5	0
*Exosurf (Protocol IND)	32	19	13	15	17	0
*Exosurf (Protocol 17)	12	9	3	5	7	0
*Exosurf (Protocol 19)	6	2	4	4	2	0
*Infasurf – Survanta	107	59	48	56	50	1
Necrotizing Enterocolitis	185	88	97	131	54	2
Single Center Nitric Oxide	17	9	8	6	11	0
*Multicenter Nitric Oxide	9	4	5	4	4	1
*RSV Immunoglobulin	9	4	5	5	4	0
*RSV Monoclonal Antibody	6	4	2	2	4	0
*rhSuperoxide Dismutase – Phase I	6	3	3	4	2	0
*rhSuperoxide Dismutase – Phase III	15	10	5	13	2	0
Permissive Hypercapnia	49	21	28	29	20	0
Vitamin A Pharmacokinetics	42	19	23	25	16	1
Hood Nitric Oxide	2	0	2	0	1	1
Gentle Touch/Massage	3	2	1	3	0	0
OBSERVATIONAL STUDIES						
*Seizure Study	159	81	78	105	52	2
*CMV Hearing Study	544	269	275	454	86	4
*Maternal Antibodies in GBS	5027	---	---	---	---	---
In Utero Cytokine Exposure	443	215	228	258	172	13
Ontogeny of Antibodies	235	106	129	120	110	5
IgG Receptor	231	117	114	141	86	4

*Denotes a multicenter study

1.4. The NICHD Neonatal Research Network - Observational Studies - 1996 to Current

Enrollment at UAB in observational studies is high compared to the other Network centers because of the large population available.

1.4.1. Generic Data Base

From 7/96 to 5/00, UAB contributed 1063 infants to the Generic Data Base, making UAB the fourth largest clinical center.

Table 1b. Gender and Race of Neonates Enrolled in the Generic Data Base

Year	Total	Male	Female	Black	White	Hispanic	Other
7/96-12/96	100	47	53	55	43	2	0
1/97-12/97	261	130	131	155	101	5	0
1/98-12/98	314	146	168	178	128	8	0
1/99-12/99	275	120	155	157	111	7	0
1/00-5/00	113	49	64	67	39	3	4

1.4.2. *In Utero* Magnesium Sulfate Exposure and Cerebral Palsy

This was an observational study to assess the association of antenatal magnesium sulfate exposure and neurodevelopmental outcome. UAB's enrollment was the third highest of the Network.

Table 1c. Gender and Race of Neonates Enrolled in the Magnesium Sulfate Exposure Study

Year	Total	Male	Female	Black	White	Hispanic	Other
1/97-12/97	110	56	54	54	53	3	0
1/98-6/98	64	25	39	30	33	1	0

1.4.3. A Study to Determine if Inflammatory Cytokines are Associated with Perinatal Brain Injury and Long Term Neurodevelopmental Handicap

Cytokine specimens have been obtained at birth, 3 ± 1 day, 7 ± 1 day, 14 ± 3 days, and 21 ± 3 days. The UAB principal investigator is chairperson of the Cytokine Protocol Subcommittee. The purpose of this study is to assess the effect of abnormal levels of pro-inflammatory and anti-inflammatory mediators on neurodevelopmental outcome in extremely low birthweight infants. UAB's enrollment is the highest in the Network.

Table 1d. Gender and Race of Neonates Enrolled in the Cytokine Study

Year	Total	Male	Female	Black	White	Hispanic	Other
3/00-6/00	29	15	14	24	5	0	0

1.5. The NICHD Neonatal Research Network - Randomized Clinical Trials - 1996 to Current

Enrollment into clinical trials at UAB usually exceeds expectations because of the large patient population, the priority given to Network protocols, and procedures in place to screen patients round the clock.

1.5.1. Randomized Trial of Vitamin A Supplementation for Extremely Low Birthweight Infants

Screening and enrollment began in July 1996. Seventy-one infants were screened for eligibility. Of these, sixty-one infants met eligibility criteria. Forty-nine infants were subsequently randomized (three infants were up for adoption, two mothers were unavailable, seven mothers denied consent). Although UAB had just joined the Network and participated for only nine of the nineteen months of recruitment, the center provided six percent (49/801) of the total enrollment in the fourteen centers and enrolled the most infants during its participation months.

Table 1e. Gender and Race of Neonates Enrolled in the Vitamin A Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
7/96-6/97	49	20	29	27	22	0	0

1.5.2. Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP Trial)

In the prophylactic indomethacin trial, UAB enrolled 60 of 65 eligible infants and exceeded projected numbers. UAB's enrollment was the highest of the Network centers. This study had a very narrow window of recruitment as infants were required to receive study medication within 6 hours of birth. The commitment of the research coordinators and research pharmacy, both providing 24-hour on call availability, were key to the successful recruitment efforts. The UAB principal investigator designed two of the secondary studies.

Table 1f. Gender and Race of Neonates Enrolled in the TIPP Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
1/97-3/98	60	26	34	29	29	2	0

1.5.3. Randomized Trial of Minimal Ventilator Support and Early Corticosteroid Therapy to Increase Survival Without Chronic Lung Disease in Extremely Low Birthweight Infants (SAVE Trial)

UAB enrolled the largest number of infants of any center (36 of 220, or 16%). Although the entry criteria required mechanical ventilation and randomization by 12 hours of age, the enrollment rate was high (82%). Enrollment into the ventilator arm within 12 hours of birth followed by steroid/placebo medication within 24 hours of birth required at least twice daily recruitment efforts by the research nurse coordinators and research pharmacists. The UAB principal investigator is the SAVE Subcommittee chairperson of the ventilation component and co-chair for the steroid component. The UAB principal investigator had a unique contribution to the SAVE trial because he was responsible for combining the steroid and ventilation components into a factorial design trial.

Table 1g. Gender and Race of Neonates Enrolled in the SAVE Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
2/98-9/98	36	19	17	14	21	1	0

1.5.4. Early Inhaled Nitric Oxide Therapy in Term or Near Term Infants with Respiratory Failure

This ongoing study utilizes a team of research coordinators, physicians, and respiratory therapists to maintain its excellence in protocol adherence. At the present time, UAB is enrolling patients in this trial at two hospitals in its center (University Hospital and Children's Hospital). Enrollment fluctuates between the third and fourth highest in the Network.

Table 1h. Gender and Race of Neonates Enrolled in the Early Inhaled Nitric Oxide Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
11/99-5/00	14	6	7	4	8	1	0

1.5.5. Randomized Controlled Trial of Parenteral Glutamine Supplementation for Extremely Low Birthweight Infants

The infants are enrolled within 72 hours of birth, with the intent of beginning total parenteral nutrition within 96 hours, necessitating weekend recruitment. Currently, 85% (56/66) of the eligible infants have been enrolled. At the time of submission, UAB's enrollment is the highest of any center.

Table 1i. Gender and Race of Neonates Enrolled in the Glutamine Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
11/99-5/00	36	19	17	14.	21	1	0

1.5.6. Randomized Controlled Trial of Induced Hypothermia for Hypoxic-Ischemic Encephalopathy in Term Infants

UAB has currently enrolled 3 of the total 19 infants, the second highest enrollment in this enrolled by the whole Network into of the Phase I Hypothermia trial. UAB utilized the support of the Alabama Society of Neonatology to enable successful early enrollment into this trial. Infants must be examined, randomized, and started on treatment prior to six hours of age. Many of these infants are born at outlying hospitals and transported to UAB. Use of the UAB transport team and referral system permits rapid transfer of these infants.

Table 1j. Gender and Race of Neonates Enrolled in the Hypothermia Trial

Year	Total	Male	Female	Black	White	Hispanic	Other
11/99-5/00	3	2	1	2	1	0	0

In summary, the clinical center at UAB has had one of the highest four enrollments in all of the observational studies and clinical trials. UAB enrolled infants in all studies performed by the whole Network. Despite UAB's interest to participate in the erythropoietin trials, UAB did not enroll patients because the sample size did not require many Network centers.

1.6. Academic Productivity of the Principal Investigator in Clinical Trials

Academic productivity in clinical trials by the proposed principal investigator, Dr. Carlo, is detailed in Section 2.1.

2. NEONATOLOGY STAFFING

The Division of Neonatology at UAB serves both inborn and outborn neonates in the level III Regional NICU at UAB. There are eight full-time neonatologists in the Division of Neonatology, all of whom are board certified in Pediatrics and Neonatal-Perinatal Medicine. The proposed principal investigator has 50% time protected for research, and the Division's other three proposed neonatology investigators have 67%, 83%, and 83% protected research time, respectively. The Division has six neonatology fellows in the fully accredited Neonatal-Perinatal Medicine Training Program. In addition, the Division includes 11 general pediatricians, who provide care of neonates in the normal newborn nursery, and a developmental pediatrician in charge of the follow-up program (see Organizational Chart in Appendix 2).

2.1. Principal Investigator

The proposed principal investigator of this project is **Waldemar A. Carlo, M.D.**, Professor of Pediatrics, Director of the Division of Neonatology, and Director of the Regional NICU at UAB and the NICU at the Children's Hospital of Alabama. Dr. Carlo will be responsible for overseeing all aspects of the project. Dr. Carlo received his medical degree from the University of Puerto Rico Medical Sciences Campus and served a pediatrics residency and chief residency at Puerto Rico's University Children's Hospital in San Juan, a program certified by the Accreditation Council for Graduate Medical Education. He completed a fellowship in neonatology at Rainbow Babies and Children's Hospital and Case Western Reserve University in Cleveland, Ohio in 1982. After completion of his fellowship, Dr. Carlo was appointed Assistant Professor of Pediatrics at Case Western Reserve University. In 1986, he was named Associate Director of the NICU at Rainbow Babies and Children's Hospital, and in 1989, he was promoted to Associate Professor of Pediatrics. Dr. Carlo became Director of the Division of Neonatology at UAB in 1991. He is co-chairperson of the National Neonatal Resuscitation Steering Committee, member of the Executive Committee of the Perinatal Section of the American Academy of Pediatrics, and member of other national professional groups and organizations including the Society for Pediatric Research, the American Pediatric Society, and the Perinatal Research Society.

During his medical career, Dr. Carlo has had extensive experience in the design, implementation, data analysis, and reporting of neonatal research including many multicenter collaborative and single center randomized clinical trials. In randomized single center trials supported by an American Lung Association grant, Dr. Carlo (PI) demonstrated that short-term use of high-frequency jet ventilation reduced airway pressures required during assisted ventilation while blood gas exchange improved (Carlo et al. 1987). In a subsequent sequential analysis trial, Dr. Carlo showed that early and exclusive use of jet ventilation in neonates with severe RDS did not significantly reduce mortality or associated morbidity (Carlo et al. 1991). These studies led to Dr. Carlo's participation in the design and execution of the multicenter National Heart, Lung, and Blood Institute High-Frequency Intervention Trial (HIFI Study Group 1989), the follow-up pulmonary study (HIFI Study Group 1990A), and the neurodevelopmental study (HIFI Study Group 1990B). A grant, with Dr. Carlo as principal investigator, funded a single center randomized trial of high vs low umbilical artery catheter placement that revealed that neonatal hypertension and other major neonatal morbidities are unrelated to catheter tip position (Stork et al. 1984). The lack of association between umbilical artery catheter position and neonatal morbidity was corroborated by the NICHD-funded multicenter Umbilical Artery Catheter Trial study in which Dr. Carlo was center PI (Umbilical Artery Catheter Trial Study Group 1992). Dr. Carlo designed a single center prospective case-controlled study to test the efficacy of computer assisted management of conventional mechanical ventilation in neonates with respiratory distress syndrome and showed that computer assisted management optimizes ventilatory management in a tertiary NICU (Carlo et al. 1986). After moving to UAB, Dr. Carlo was clinical center PI for the Infasurf vs Survanta Randomized Clinical Trial (Bloom et al. 1997), an investigator in the single center pilot study of inhaled nitric oxide (Barefield et al. 1996), and clinical center PI for the rhSOD phases I and III randomized trial (Davis et al. 1997; Davis et al. 1999). Dr. Carlo was the senior investigator of two single center randomized clinical trial at UAB to test the effect of fast vs slow increases in feedings on the incidence of necrotizing enterocolitis (Rayyis et al. 1999) and to test the feasibility of permissive hypercapnia (Mariani et al. 1999). In addition, as Center PI for the current NICHD, Dr. Carlo has participated in the Network trials and serves as chairperson of three Network studies (minimal ventilation to reduce chronic lung disease, cytokines in extremely low birth weight infants, and sedation in ventilated infants). In addition, Dr. Carlo has published manuscripts on three other therapeutic clinical trials with crossover designs, a case-controlled single center study, 22 clinical studies with crossover design that evaluate the effect of various interventions on short-term physiologic outcomes in human neonates, and nine observational studies in neonates. Dr. Carlo has also authored many manuscripts on laboratory-based *in vivo* and *in vitro* experiments focused on developmental control of breathing, ventilation, gas exchange, and lung injury. He is currently PI of the Perinatal Outreach Education Grant that serves to enhance the education and practice of perinatal healthcare providers in the State of Alabama. Dr. Carlo collaborates with several other investigators in various departments within the University. He is an investigator in the Patient Outcome Research Team (PORT) of the Division of Maternal-Fetal Medicine of the Department of Obstetrics and Gynecology and the NICHD Perinatal Emphasis Research Center (PERC) Project IV Neonatal Systemic Inflammatory Response Syndrome: Role of *In Utero* Cytokine Exposure of the UAB Rural Perinatal Center (NICHD). Dr. Carlo is the designated neonatologist in the current NICHD Maternal-Fetal Medicine Units Network at UAB and in the application being submitted.

Since arriving at UAB in 1991, Dr. Carlo has been instrumental in revitalizing the Division of Neonatology and the Regional NICU. The number of faculty members has increased from five to eight, allowing for more protected research time. The Regional NICU has been reestablished as the perinatal tertiary referral center for the State, assuring a large high-risk inborn population and a large neonatal referral base, resulting in a 12% increase in the number of very low birth weight infants admitted. The NICU at Children's Hospital of Alabama has increased its average daily census by 50% since Dr. Carlo's arrival. Dr. Carlo developed the UAB NICU Network, a county- and region-based referral network of five community NICUs (referrals from over 10,000 additional deliveries) that collaborate on patient care, research, and education while receiving neonatal coverage by the Division of Neonatology at UAB. The Regional NICU data base has been expanded to include patients transferred to the surgical NICU. Dr. Carlo has worked to develop strong investigational, clinical, and educational ties to the Division of Maternal-Fetal Medicine. Collaborations have been established with 12 research laboratories within the Department of Pediatrics and other departments in the Medical School and throughout the University. Under Dr. Carlo's leadership, the Graduate Medical Education-accredited Neonatal-Perinatal Medicine Training Program has had an increase in the number of fellowship applicants interviewed from less than five per year to over 15 per year from 1990 to 2000. The number of fellows has increased from two in 1990 to six fellows currently. Dr. Carlo successfully competed for the NICHD Cooperative Neonatal Research Network grant for the years 1996 to 2001. As documented in Sections 1.4 and 1.5, Dr. Carlo's enthusiastic and thorough participation in the Neonatal Network has resulted in full participation of the UAB clinical center. Dr. Carlo recently completed a new human subject education training program that meets the new Required Education in the Protection of Human Research Participants policy from the NIH. Dr. Carlo is aware of the New Steps to Protect Participants in Clinical Trials announced by Mr. Clinton. Dr. Carlo's training, extensive clinical track record, scholarly accomplishments, and demonstrated administrative skills in many clinical research trials and in divisional development document his qualifications to direct a clinical center of the NICHD Neonatal Network. Dr. Carlo has 50% protected time for research.

2.2. Other Neonatologists in the Division Listed as Investigators in this Proposal

Joseph B. Philips, III, M.D., is currently Professor with a triple appointment in Pediatrics, Obstetrics and Gynecology, and Physiology and Biophysics. Dr. Philips is the Director of the Neonatal Physiology Research Laboratories. He received his medical degree from the University of North Carolina at Chapel Hill and served two years as a pediatric resident at Mount Sinai Hospital with a final year at Duke University School of Medicine. He completed the neonatology fellowship at the University of Florida at Gainesville. Dr. Philips has spent his entire professional career at UAB, contributing markedly to laboratory-based research. He has published extensively with particular emphasis on regulation of pulmonary vascular tone and persistent pulmonary hypertension. Dr. Philips served as co-principal investigator for the NICHD Neonatal Network from 1986 to 1990. Dr. Philips took a sabbatical leave at the University of Virginia, funded by a National Research Service Award, where he learned and used cellular and molecular techniques applicable to these lines of investigation. His current areas of research interest include molecular and cellular biology, regulation of pulmonary vascular resistance, peptide growth factors in pulmonary vascular remodeling, and hemodynamic effects of experimental sepsis. Dr. Philips collaborates with other investigators within various divisions and departments of the University. He is PI of the NICHD grant Role of IgG Receptor Isoforms in Neonatal Infections, a study to determine the role of genetic variability of IgG receptors in infants with late onset sepsis and the NICHD multicenter study to determine protective levels of maternal antibody against early onset of invasive group B streptococcal disease in neonates. Dr. Philips' experience and expertise in basic and clinical research are important assets to the Division. Dr. Philips has 67% protected time for research.

Namasivayam Ambalavanan, M.D. is Assistant Professor of Pediatrics. He received his medical degree from the JIPMER, India, and served three years as a pediatric resident at PGIMER, India, as well as an additional year of pediatric residency at the University of Alabama at Birmingham. He completed the neonatology fellowship at the University of Alabama at Birmingham in 1997. Dr. Ambalavanan has experience in both laboratory-based research and neonatal clinical trials. He is studying the cellular mechanisms underlying vascular remodeling in persistent pulmonary hypertension of the newborn and the role of newer therapies in persistent pulmonary hypertension. He was recently awarded the Young Investigator Award by the Southern Society of Pediatric Research for his research on delivery of nitric oxide by oxygen hood. His clinical research has dealt with neonatal feeding practices, vitamin A pharmacokinetics, neural networks, inhaled nitric oxide, and neonatal analgesia and sedation. In association with Dr. Carlo, he has designed a randomized controlled trial for the evaluation of analgesia in mechanically ventilated neonates that has been approved by the Steering Committee of the NICHD Neonatal Network. Enrollment is expected to start within the next year. Starting this fall, Dr. Ambalavanan will be enrolled in the NIH-sponsored UAB Clinical Research Training Program. In a short time, Dr. Ambalavanan has demonstrated a strong commitment to high quality clinical research. Dr. Ambalavanan has 83% protected time for research.

Robert Schelonka, M.D. is Assistant Professor of Pediatrics. He received his medical degree from Case Western Reserve School of Medicine and completed postgraduate training in pediatrics and neonatology at Wilford Hall Medical Center in 1997. Dr. Schelonka has experience in both clinical and laboratory-based research. His research focus is the ontogeny of the immune system, particularly with regard to the development and maturation of T lymphocytes. His clinical research has been in the area of newborn infectious diseases. He received the American Academy of Pediatrics Howard Johnson and Andrew Margelith research awards for his work in predicting newborn sepsis and determining the sensitivity of blood culture in low colony count bacteremia. Dr. Schelonka has 83% protected time for research.

2.3. Other Full-Time Neonatologists in the Division at UAB

Carl H. Coghill, III, M.D., is Associate Professor of Pediatrics and serves as Director of the Clinical Section and Medical Director of the NICUs at The Children's Hospital of Alabama and Baptist Medical Center-Montclair. He received his medical degree from the Medical University of South Carolina and served his residency in pediatrics at Bowman Gray School of

Medicine. Dr. Coghill completed his neonatology fellowship at Vanderbilt University and has been with UAB since 1991. His research interests include clinical trials, high frequency ventilation, artificial intelligence, and computer applications in clinical neonatology research.

James L. Haywood, M.D., is Associate Professor of Pediatrics and serves as Medical Director of the NICUs at Baptist Medical Center-Princeton and Shelby County Medical Center. He received his medical degree from UAB and served a pediatric residency at the University of Alabama School of Medicine. Dr. Haywood completed a neonatology fellowship at Vanderbilt University. He has been at UAB since 1991. His research interests include perinatal epidemiology, impact of physician knowledge on practice, clinical trials, and patent ductus arteriosus. Dr. Haywood is an investigator in the PORT grant.

Virginia Karle, M.D., is Assistant Professor of Pediatrics and serves as Medical Director of the NICU at Medical Center East. She received her medical degree from the Medical College of Georgia and served a pediatric residency at The Children's Hospital Medical Center, University of Cincinnati. She completed a neonatology fellowship at Children's National Medical Center, George Washington University in 1993 and joined UAB that year. Her research interests include ECMO, persistent pulmonary hypertension of the newborn, and inhaled nitric oxide.

Elaine Barefield St. John, M.D., is Associate Professor of Pediatrics and serves as chairperson of the Perinatal Mortality Committee. She received her medical degree and served her residency in Pediatrics at the University of Alabama at Birmingham. After completing the neonatology fellowship at Brown University in 1987, Dr. Barefield St. John returned to UAB to begin her professional career. Dr. Barefield St. John was center PI and a member of the national Steering Committee for the Ohmeda inhaled nitric oxide multicenter randomized clinical trial. She was center PI of the two multicenter randomized clinical trials of intravenous immunoglobulin in infants at risk for respiratory syncytial virus. Dr. Barefield St. John is an investigator in the PORT grant.

2.4. Other Neonatologists with Clinical Appointments

In addition to these eight full-time neonatologists in the Division, three board-certified neonatologists have clinical appointments within the Division and practice in Birmingham. **Dr. Martha Strange** is Medical Director at Brookwood Women's Medical Center, **Dr. Terry Bierd** is Medical Director at St. Vincent's hospital, and **Dr. Santosh Khare** is Director of Neonatal Services at Cooper Green Hospital, the county hospital for indigent patients. These three hospitals have over 7,000 total deliveries per year and refer their sickest neonates to the Regional NICU at UAB. Together with the UAB NICU Network, these hospitals constitute the Birmingham-based network of NICUs that refer selected neonates to the Regional NICU at UAB.

2.5. Pediatricians Within the Division of Neonatology

Eleven pediatricians provide normal newborn nursery care and one developmental pediatrician works in the high-risk follow-up program at UAB in addition to their other functions as general pediatricians in the Department of Pediatrics at UAB. **Carolyn Ashworth, M.D.,** Director of the Newborn Nursery at UAB, is Professor of Pediatrics. **Kathleen Nelson, M.D.,** is Professor of Pediatrics, Associate Dean of the School of Medicine, and Medical Director of the High-Risk Newborn Follow-Up Program at UAB. She has had extensive experience in developmental evaluation and follow-up studies, as she has directed the Neonatal Intensive Care Follow-Up Program at Birmingham since 1977. An additional pediatrician, **Katherine Buchan, M.D.,** works full-time for the Division, providing direct patient care in the intermediate nursery.

3. AVAILABLE POPULATION

An average of 945 ill neonates per year were admitted to the Regional NICU at UAB during the past five years. Outborn infants accounted for 16.4% of the NICU admissions. The patient population is similar to that of many large academic health centers and includes a broad representation of birthweights, gestational ages, racial/ethnic groups, admitting diagnoses, obstetrical parameters, and socioeconomic/payment classes. A computerized data base that includes patient characteristics, demographics, and clinical outcome variables is used to carefully record and track the patient population. Strategies are in place to maintain access to a large number of neonatal patients. The proportions of infants by racial/ethnic group and gender enrolled in trials and observational studies were reported in Sections 1.3, 1.4, and 1.5. These proportions of infants are similar to that of the infants admitted to the Regional NICU (Section 3.3.1).

3.1. Admissions Per Year

A major strength of this proposal is the number of admissions at the Regional NICU at UAB, which exceeds the minimum of 500 per year required by the Cooperative Multicenter Neonatal Research RFA. Since 1995, when this center joined the NICHD Neonatal Intensive Care Network, the number of admissions to the Regional NICU at UAB has averaged 945 per year with a range of 834 to 1053 (Table 2). The number of admissions during the last three years has been above the five-year average of 945.

Table 2. Number of Admissions Per Year to the Regional NICU at UAB

Year	1995	1996	1997	1998	1999	Average
Admissions (n)	880	834	976	1053	983	945

3.1.1. Birthweight and Gestational Age Distribution of the Neonates Admitted

The proportions of admitted neonates in each birthweight and gestational age subgroup have remained stable over the last five years. An average of 29% of the admitted neonates have been very low birthweight (≤ 1500 g) infants while 33% had weights of 1501 to 2500 g (Figure 1-A). Sixty-six percent of the neonates were premature (≤ 36 week) and all gestational ages have been well represented (Figure 1-B).

Figure 1. Distribution of Neonates Admitted to the Regional NICU at UAB

Figure 1-A. By Birthweight Subgroups

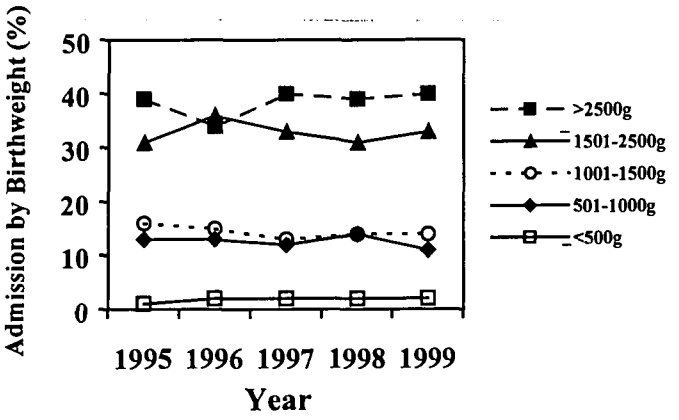
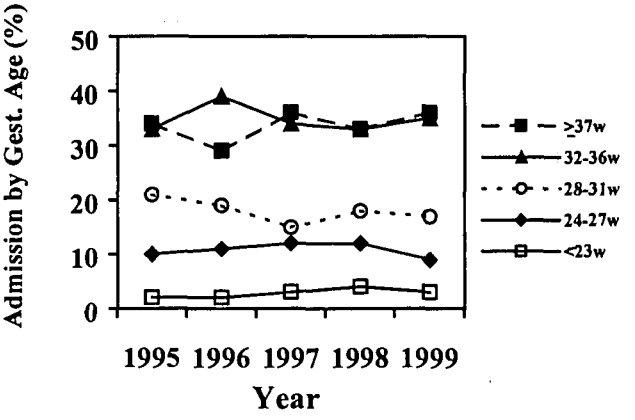


Figure 1-B. By Gestational Age Subgroups



3.1.2. Inborn/Outborn and Referral Patterns

The percentage of outborn admissions (average 16.4%, range 13.3 to 20.5%) and the referral patterns have remained steady despite current changes in health care largely because the Perinatal Center at UAB serves the entire State of Alabama and has ties to all obstetrical, pediatric, and neonatal practices. Both neonatal and maternal referrals are performed routinely in order to deliver optimal patient care and provide complete services to the statewide perinatal health care network. A network of health departments and county hospital clinics, as well as private obstetricians, general and family physicians, pediatricians, and neonatologists consult UAB physicians via a dedicated 800 line. Depending on the timing of the identification of the high-risk factors, women may be referred during preconception, early or late pregnancy, or during labor. Neonatal referrals are received from all level I, II, and III services throughout the State. All thirteen level III NICUs and regional NICUs in Alabama refer neonates with selected diagnoses (e.g., congenital heart disease, persistent pulmonary hypertension, major surgical disorders, and major congenital anomalies) directly to the Regional NICU at UAB. In addition, selected neonates and pregnant women with highly complex medical or surgical conditions are referred from areas in bordering states. This statewide perinatal network has allowed the Regional NICU at UAB to maintain the large number of high-risk admissions and a stable percentage of outborn neonates that averaged 16.4% during the last five years (Table 3).

Table 3. Inborn/Outborn Status of Neonates Admitted to the Regional NICU at UAB

Year	1995	1996	1997	1998	1999	Average
Inborn (%)	87	84	82	85	80	84
Outborn (%)	13	16	18	15	20	16

The percentage of outborn neonatal admissions has been consistently within the stated requirement (less than 30%) and provides an appropriate mix of neonates with varying diagnoses (see 3.3.2) and degrees of illness severity. Furthermore, the percentage of outborn neonates has been stable throughout the various weight groups and gestational ages over the last five years.

3.2. Strategies to Maintain Access to an Adequate Number of Neonatal Patients

Even though the number of admissions to the Regional NICU at UAB is well above the minimum and a decline in admissions is not expected, the Division of Neonatology has developed a strategic clinical services plan to assure a large patient base. The Division also provides neonatal care in six NICUs in Birmingham, including The Children's Hospital of Alabama NICU and five NICUs in community hospitals. These six NICUs combined had an average of 666 admissions per year during the last five years, excluding transfers from the UAB Regional NICU. These six NICUs are not part of this proposal as the available patient population at the Regional NICU at UAB is sufficiently large. However, this well-organized perinatal health care system assures an adequate number of maternal and neonatal referrals to UAB. A letter from the medical director of these NICUs is included (Appendix 3). Patient care in each of these units is provided by a large group of experienced neonatal nurse practitioners that are supervised directly by members of the Clinical Section of the Division of Neonatology. Residents and neonatology fellows do not rotate through the community hospitals' NICUs. In order to protect research time and other academic activities, this extra clinical commitment is not shared equally among the neonatologists in the Division. The proposed four full-time neonatologists in this grant application only rotate through the Regional NICU at UAB and The Children's Hospital NICU. They have sufficient protected research time, committing 50% to 83% of their time to research. Three other NICUs in Birmingham, as well as each of the four other NICUs in Alabama have affirmed their interest to collaborate in Network research if it is necessary to have access to their patient population (Appendix 3). The Alabama Society of Neonatology, which includes among its members all the practicing neonatologists in the State, supports this collaboration (Appendix 3).

3.3. Patient Population

3.3.1. Demographics

The patient population served by the Regional NICU at UAB is similar to that of many large academic health centers in the United States. Since 1995, the racial/ethnic make-up of the admitted neonates has been as follows: Black 50%, White 47%, Hispanics 2.6%, and others 0.4% (Figure 2-A). The Native American population in Alabama constitutes approximately 0.5% of the general population. However, because of interracial marriage, they usually consider themselves Caucasian and are presently

coded according to their preference. The number of male neonates requiring admission to the Regional NICU consistently has exceeded the number of females. Male infants comprise an average of 53% of the admissions (Figure 2-B).

Figure 2-A. Race of Neonates Requiring Admission to the Regional NICU at UAB

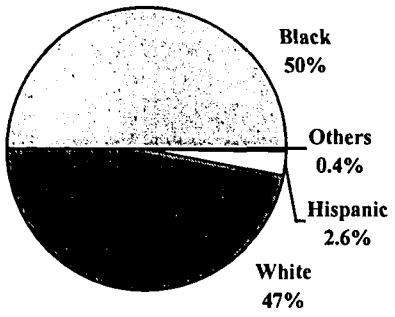
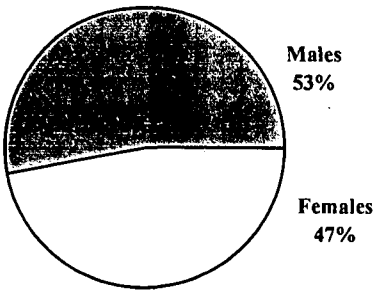


Figure 2-B. Gender of Neonates Requiring Admission to the Regional NICU at UAB



3.3.2. Admitting Diagnoses

The list of admitting diagnoses is broad, but as expected, strongly dependent on the birthweight, gestational age, and inborn/outborn status of the neonate. A representative list of admitting diagnoses for a recent month is included in Appendix 4.

3.3.3. Obstetric Parameters

The mothers of neonates requiring admission to the Regional NICU at UAB have obstetric characteristics typical of a high-risk population (Table 4).

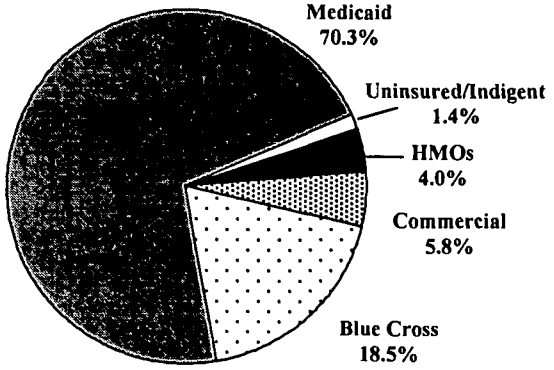
Table 4. Obstetrical Parameters of the Admissions to the Regional NICU at UAB from 1995 to 1999

	Total	Percent
Gestational age ≤ 34 weeks	2885	61
Cesarean Section	1695	36
Chorioamnionitis	667	14
Maternal hypertension	971	21
Maternal diabetes	306	6

3.3.4. Payment Status

As in many NICUs in the United States, the lowest socioeconomic classes are disproportionately over-represented in the Regional NICU at UAB. Over two-thirds (70.3%) of the neonates have medical coverage under Medicaid, and 28.3% are privately funded (Figure 3). Admission and care at the Regional NICU at UAB are performed regardless of the payment status. Clinicians are not aware of the payment status. The same neonatologists and staff care for all patients. Enrollment of neonates into the clinical studies is completely independent of race, gender, socioeconomic status, and payment status.

Figure 3. Payment Status of Neonates Admitted to the Regional NICU at UAB



3.3.5 Outcome

Data on survival to discharge for all infants admitted from 1995 to 1999 are provided by birthweight (Figure 4-A) and gestational age (Figure 4-B), in the subgroups usually reported by the NICHD Neonatal Network. For specific comparisons with some published data, survival to discharge is also reported by 100 g increments and by each week of gestation in Appendix 5a. Compared to the previous five years, survival to discharge has increased for each of the weight subgroups ≤ 1250 g and for each of the gestational age subgroups ≤ 36 weeks during the 1995 to 1999 period. (Appendix 5b).

Figure 4. Survival to Discharge of Neonates Admitted to the Regional NICU at UAB for the Years 1995 to 1999.

Figure 4-A. By Birthweight Subgroups

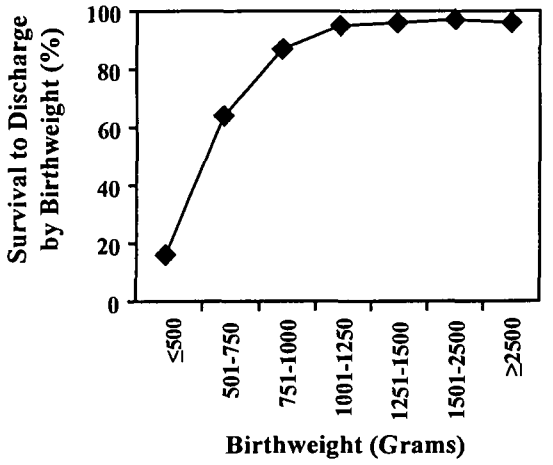
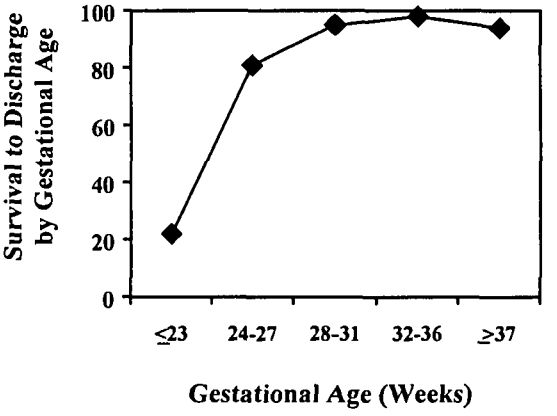


Figure 4-B. By Gestational Age Subgroups



4. MATERNAL FETAL MEDICINE UNIT

The Division of Maternal-Fetal Medicine (MFM) in the Department of Obstetrics and Gynecology at UAB has a large perinatal program that includes delivery of many high-risk pregnancies. The Division is nationally recognized as a leader in perinatal research, patient care, and education and is one of the NICHD MFM Units Network clinical centers. Ten MFM specialists, who have demonstrated continued creativity and excellence in clinical research, patient care, and all academic endeavors, staff the large high-risk perinatal service. A long-standing history of collaborative research between the Divisions of MFM and Neonatology has led to important accomplishments in research, with particular emphasis in clinical trials. Data collected by each Division on their patients is shared through their respective data bases. Collaborative research, one of the foremost goals for the two Divisions, has led to extensive cooperation and close interaction in numerous randomized clinical trials and other clinical studies in the past years. Close communication is maintained by daily, weekly, and monthly formal and informal patient care-oriented activities. Quarterly meetings of clinical investigators from both divisions and additional meetings as needed are held to assure close interaction and prevent conflict in research endeavors, particularly as both divisions are current members of the respective NICHD research networks. The scholarly MFM faculty and large high-risk delivery service provide a unique environment and opportunity for a clinical center of the NICHD Neonatal Network.

4.1. Maternal Fetal Medicine Unit

The Perinatal Center at UAB provides high-risk and comprehensive prenatal care through a network of eight Jefferson County antepartum public health clinics, the Health Department clinics in two surrounding counties, and the Obstetrical Complication Clinic at UAB. About 4,000 women per year receive prenatal care through this system. There are approximately 450 additional maternal-fetal transports per year. Deliveries are performed at two services within the UAB Medical Center. The high-risk delivery service at University Hospital is contiguous to the Regional NICU and since 1996 has had an average of 3,133 deliveries per year. The low-risk delivery service at Cooper Green Hospital has had an average of 1,399 deliveries over the last four years yielding a total of 4,532 deliveries per year in the Center. Care is provided by ten MFM specialists (see below), three MFM fellows, ten obstetrical nurse practitioners, four certified nurse midwives, 68 nurses, and 28 obstetrics/gynecology residents. The accredited MFM and obstetrics/gynecology programs provide comprehensive training to fellows and residents.

4.2. Maternal Fetal Medicine Subspecialists

The Division of MFM has ten full-time MFM subspecialists, eight of who are board certified in MFM and two who are board eligible.

William Andrews, M.D., is Professor of Obstetrics and Gynecology and Director of the Division of MFM at UAB. Dr. Andrews, who has excelled in the design and execution of several federally-funded randomized clinical trials and studies, will be the designated obstetrician in the present grant application. Details of his academic productivity are included in Section 4.4 (Designated Obstetrician) below.

John C. Hauth, M.D., is Professor of Obstetrics and Gynecology, Director for the Center for Research in Women's Health, and Chairman of the Department of Obstetrics and Gynecology. Dr. Hauth has extensive experience in clinical and laboratory research and has designed and conducted numerous randomized clinical trials in maternal fetal medicine. He has a national/international reputation as a clinical investigator in maternal fetal medicine and has published extensively on operative obstetrics, preeclampsia, and the role of maternal infection in spontaneous preterm labor and delivery. He will be an editor for the next edition of *Williams Obstetrics*. Currently he is the PI of the UAB Rural Perinatal Emphasis Research Center (PERC), the NIDR/NICHD Periodontal supplement to the PERC award, the UAB participation in the NICHD Maternal Fetal Medicine Units Network, and the NICHD OB/GYN Faculty Research Career Development Program. Additionally, a grant application for the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) is currently pending final approval..

Robert Goldenberg, M.D., is the Charles F. Flowers Professor of Obstetrics and Gynecology, and Professor of Public Health and Preventive Medicine at UAB. As Director of the Center for Obstetric Research, Dr. Goldenberg has been responsible

for several major population-based research projects including the Alabama portion of the March of Dimes multicenter project on prematurity prevention, 1982-1986, and the Small for Gestational Age study funded by the NIHCD from 1984 to the present. He also organized and directed the NICHD Maternal Fetal Medicine Units Network's Preterm Prediction Study, which has been that Network's most productive effort to date. He was also PI for a large AHCPR funded patient Outcome Research Team (PORT) Grant to study the effectiveness of various obstetric practices in preventing low birthweight and its sequelae. Dr. Goldenberg has been a member of the Institute of Medicine since 1997, has served as chairman of the Pediatrics and Ob-Gyn sections of the Institute of Medicine since 1998, and has been a member of the Committee on Improving Birth Outcomes in Developing Countries since 1999. Dr. Goldenberg has published more than 300 journal articles predominantly related to preterm delivery and growth retardation.

Dwight Rouse, M.D., is Associate Professor of Obstetrics and Gynecology at UAB. Dr. Rouse will be the PI in the Competitive Renewal Application of the NICHD Maternal Fetal Medicine Units Network. Dr. Rouse has extensive experience in clinical trials dating back to his residency when he helped design, conduct, and analyze a placebo-controlled double-masked trial of vitamin B_6 for the nausea and vomiting of pregnancy. Since then he has performed a randomized trial of management of arrested labor, and a placebo-controlled randomized clinical trial of chlorhexidine vaginal irrigation for the prevention of peripartal infection with the enrollment of over 1000 patients. This last trial served as the basis for a successful R01 application to further evaluate a modified chlorhexidine vaginal irrigation intervention. Dr. Rouse currently serves as the subcommittee chairman (PI) of the jointly funded (NICHD-NINDS) MFM Network BEAM trial, a randomized double-masked placebo-controlled clinical trial designed to evaluate whether prophylactic magnesium sulfate, given to women between 24 and 31 weeks gestation and imminent delivery, reduces the incidence of death or moderate to severe cerebral palsy (diagnosed at 24 months) in their children. Dr. Rouse is the recipient of a five-year (7/2000-6/2005) Mid-Career Investigator Award in Patient-Oriented Research. Dr. Rouse is Medical Director of the UAB Obstetrics Complications Clinic. Dr. Rouse's national clinical activities include serving on the Technical Expert Advisory Committee of the Agency for Healthcare Policy and Research-funded Preterm Labor Evidence Report (10/98-1/99) and, at the request of the American College of Obstetrics and Gynecology Obstetric Practice Committee, authoring practice guidelines on Antepartum Fetal Surveillance.

Richard Davis, M.D., Professor of Obstetrics and Gynecology and Past Director of the Division of Maternal Fetal Medicine, supervises all obstetrical ultrasounds and the four obstetrical scanning laboratories at UAB. He has been an active investigator and collaborator in most obstetrical clinical trials performed at UAB. He is fully supportive of all Neonatal Network and MFM Network studies. **Cynthia Brumfield, M.D.**, is Professor of Obstetrics and Gynecology and Medical Director of the Obstetric Service at UAB. **Katherine Wenstrom, M.D.**, Associate Professor of Obstetrics and Gynecology and Director of Prenatal Diagnosis and Ultrasound, is particularly interested in genetics. She is board certified in Medical Genetics in addition to MFM, and is Director of the Medical Genetics Residency Program. **John Owen, M.D.**, Associate Professor of Obstetrics and Director of the MFM Fellowship Program, is Director of In-Hospital Research. His research interests are computer applications in obstetrics, fetal surveillance techniques, prenatal diagnosis, and targeted ultrasound. **Alice Goepfert, M.D.**, is Assistant Professor of Obstetrics and Gynecology. She is one of the four NICHD Women's Reproductive Health Research Scholars at UAB and is a participant in the UAB Clinical Research Training Program. Her research interest is obstetrical infections and mucosal immunology. **Debora Kimberlin, M.D.**, is Assistant Professor of Obstetrics and Gynecology and Director of the Prematurity Prevention Clinic at UAB. Her primary research interest is prevention of prematurity and obstetrical infections. **Barbara Hogg, M.D.**, is Assistant Professor of Obstetrics and Gynecology. She has recently completed the fellowship at UAB and her research interest is preeclampsia.

4.3. Cooperation Between the Divisions of Neonatology and Maternal Fetal Medicine

The Divisions of Neonatology and MFM at UAB have a long standing tradition of cooperation and collaboration in academic activities, including commitment to foster perinatal research, daily combined rounds in the high-risk delivery service, weekly Perinatal Grand Rounds, monthly Perinatal Mortality Committee conference, quarterly combined divisional meetings, and a strong collaboration on data base management. Informal communication and exchange is facilitated by the proximal location of the Divisions' offices in the Hillman Building at UAB.

The two divisions have agreed to collaborate in all research, particularly NICHD Network protocols. Despite very active Neonatal and MFM NICHD-sponsored networks, there has not been conflict in enrollment of patients. Recognizing the potential for both collaboration and conflict as a result of both Divisions having an NICHD network clinical center, Dr. Carlo and Dr. Hauth (in his role of MFMU Network PI) have been proactive in their interactive approach. As occurs at the Network level where designated Network PIs serve as liaisons to the respective companion Network, locally the two PIs meet on a periodic basis to discuss ongoing and planned protocols, to facilitate both MFM and neonatology research, and to resolve potential conflicts (e.g., deciding who will have the right of first approach to a pregnant woman who is eligible for a project of the MFM Network and whose fetus is likely to become eligible for a project of the NICU Network). Similarly, the NICU Nurse Coordinator, Monica Collins or Shirley Cosby, and the MFMU Nurse Coordinator, Allison Northen, meet periodically to discuss the pragmatic aspects of research conduct. As intended, the result has been to foster a collaborative rather than competitive approach to MFM and NICU research. There have been synergistic effects because of increased collaboration between MFM and neonatology attendings resulting in superior performance by both groups. For example, neonatal sepsis-like syndrome related to *in utero* cytokine exposure is a project of the PERC grant that involved MFM and NICU input into the design, shared data retrieval duties, and a joint analytic strategy. Dr. Carlo's contribution was essential in this MFM grant application. In turn, Dr. Andrews' input was instrumental in the technical aspects of the NICU Network Cytokine Study. Likewise, for the MFMU Network BEAM Trial, in-hospital neonatal evaluation and follow-up of infants until two years of age are being accomplished with the resources and personnel of the NICU and the High Risk Infant Follow-up Program. As a more recent example, Dr. Carlo sought the advice of

Dr. Rouse on a pilot NICU Network trial of early versus delayed umbilical cord clamping in the prematurely delivered infant. Because of Dr. Rouse's prior research in this area, they were able to outline a strategy for the successful implementation of this pilot trial. Furthermore, the use of definitions by MFM specialists and neonatologists consistent with those of the NICHD Neonatal Network has facilitated collaborative research. In summary, as a result of the collaborative MFM-NICU approach to perinatal research, UAB has been a leading recruiter (and on many protocols, the leading recruiter) in both NICU and MFMU Network protocols

4.3.1. Clinical Care

The Divisions of Neonatology and MFM communicate informally on a daily basis to optimize patient care, particularly during early postnatal life. The neonatologist, MFM specialist, and fellows on clinical service meet at a defined time every morning in the labor and delivery suite to discuss impending high-risk deliveries and other hospitalized pregnant women. Updates on the status of the neonates recently admitted to the Regional NICU are provided to the MFM specialists. Combined maternal and neonatal management discussions are held as part of the weekly Perinatal Grand Rounds. Attended by neonatology and MFM specialists and fellows, a pediatric pathologist, a perinatal anesthesiologist, perinatal/neonatal nurses, and quality improvement staff, the Perinatal Mortality Committee is a forum for thorough multidisciplinary review of stillbirths and neonatal deaths. The quarterly meeting of faculty members in both Divisions provides opportunities to resolve differences and facilitate long term planning regarding patient care, clinical research, and education.

4.3.2. Maintenance of a Data Base

The Division of MFM maintains the Obstetrical Automated Record (OBAR) system, which is an essential and primary component of the patient data bases. The OBAR's primary goal is to provide up-to-date computer-based prenatal, labor and delivery, and postnatal data wherever obstetrical patients are seen in the Jefferson County Department of Health and/or the UAB obstetric health care systems. Upon registration at any county health department clinic or at University Hospital, an OBAR encounter form is completed and entered into the centralized computer system. Data collected include medical and obstetric history, blood pressure, weight, height, type of work, marital status, race, fundal measurements, hematocrit, proteinuria, etc. Extensive amounts of delivery data are added immediately postpartum while appropriate newborn data are entered following infant discharge. Copies of the OBAR forms are included in Appendix 6.

The OBAR System also provides a means of tracking, analyzing, and reporting the vast amount of data collected on each patient seen in the Jefferson County Health Department and the Division. In addition, prenatal and intrapartum data are provided to the neonatologists or pediatricians at birth on hard copies and the data are available on line to the neonatologists in the Regional NICU. A description of this system, along with its many advantages for patient care and clinical research, has been published (Wirtschafter et al. 1982). Virtually every item of prenatal, intrapartum, and immediate postpartum data has been computerized and is available for population characterization, outcome analysis, and other purposes. The OBAR historical data base contains almost 1000 coded items per mother-infant dyad on more than 75,000 pregnancies collected continuously since 1979. Over 4,000 additional pregnancies are entered into the system each year. All completed pregnancies can become part of a research data base, which is in Statistical Analysis System (SAS) format and easily analyzed. These data are available for population characterization and data analysis.

Each public health department maternity or Division clinic has personnel to enter patient information into the computerized data base usually within 24 hours of each prenatal visit. A data base manager is responsible for all research data entry, quality control, and reports of completed and ongoing study results. A full-time data analyst with expertise in computerized data base studies in maternal-child health epidemiology and pregnancy outcome conducts biostatistical analyses. The OBAR system is an essential resource for the ongoing collaborative research between the Divisions of Neonatology and MFM.

4.3.3. Research Productivity

The close relationship between the Divisions of Neonatology and MFM in clinical care is paralleled in the research area. Past and present research collaborations have focused on infectious diseases, intrauterine growth retardation, clinical trials, perinatal epidemiology, and long term follow-up. Major areas of current collaboration in research include: NICHD-funded multicenter study on maternal antibody in early neonatal group B streptococcal infection (Dr. Philips PI, Rouse et al. 1998), NIH-funded studies on ureaplasma, NICHD-funded randomized trial of zinc supplementation on pregnancy outcome, and Patient Oriented Research Team (PORT) studies on cost of neonatal care (St. John et al. 2000), physician and nurses attitudes regarding neonatal outcome (Haywood et al. 1994; Haywood et al. 1998; Morse et al. 2000), and referral to level III nurseries (Bronstein et al. 1995). Drs. Carlo, Barefield St. John, and Haywood are investigators in the PORT grant. In addition, the neonatologists provide data on the neonates of the mothers participating in any MFM study that requires data collection in the offspring. A Perinatal Emphasis Research Center (PERC) grant on infection and prematurity funds a study on cytokine analysis in preterm infants conducted by Drs. Andrews (MFM) and Carlo.

4.4. Designated Obstetrician

The designated obstetrician is **William Andrews, M.D., Ph.D.** Dr. Andrews is Professor of Obstetrics and Gynecology, Director of the MFM Division, and Director of the Infectious Disease Research Laboratory. He is board certified in maternal fetal medicine. His research interests are obstetrical and perinatal infections including infectious etiologies of preterm birth and the role of cytokines in fetal and neonatal systemic inflammations. Dr. Andrews has served as consultant for the cytokine response syndrome protocol developed by Dr. Carlo for the NICHD Neonatal Network. Dr. Andrews' ongoing research projects include: 1) investigations of *C. trachomatis* in the urine of pregnant women to evaluate the role of this sexually transmitted disease in preterm birth; 2) investigations of cervical/vaginal fetal fibronectin to identify women at risk for preterm birth and to target this population of women for interventions designed to prevent preterm birth; 3) an investigation of the role of upper genital

tract infection and inflammation in the development of early onset systemic inflammatory response syndrome (sepsis-like syndrome) in neonates; 4) numerous ongoing microbiological studies of the association between genital tract infection and/or inflammation with spontaneous early pregnancy loss and preterm birth; 5) evaluations of vaginal metabolic and biochemical correlates with bacterial vaginosis and their independent association with spontaneous preterm birth; 6) investigations of the epidemiology and natural history of altered vaginal flora and the association of this condition with psychosocial status, sexual, and personal health behaviors; and 7) ongoing investigations of vertical transmission of genital herpes simplex virus and potential obstetrical interventions related to this viral infection. Dr. Andrews is principal investigator of the Fetal Fibronectin Protocol being conducted by the Maternal Fetal Medicine Network. In addition, the Obstetrics and Gynecology Infectious Disease Research Laboratory under the direction of Dr. Andrews continues to support multiple research endeavors including projects underway exclusively at UAB as well as multicenter, international, and NICHD Maternal Fetal Network projects. Dr. Andrews also serves as a consultant, advisor, and co-investigator for the International Clinical Epidemiology Network and is currently participating in a multicenter international study of the frequency and impact of altered vaginal flora on preterm birth. He is an associate director of the UAB Ob/Gyn Faculty Research Career Development Program and participates in the mentoring and career development of junior faculty. Because of his outstanding record as a clinical investigator and a collaborator in neonatal research, Dr. Andrews is uniquely qualified to serve as the designated obstetrician of this Neonatal Network proposal. Drs. Carlo and Andrews interact closely in patient care, research, and education. Dr. Andrews is very supportive of the obstetrical/neonatal academic and scholarly efforts at UAB and has expressed his unconditional commitment to collaborate with the neonatologists in the protocols developed by the Neonatal Network. A letter of support from Dr. Andrews is in Appendix 7.

4.5. Organization and Service Load of the Maternal Fetal Medicine Division

4.5.1. Research Activities

The MFM Division at UAB is very active in the design, implementation, and completion of randomized clinical trials, observational studies, epidemiological research, and laboratory-based experimentation. The excellence of their research has led to extensive federal funding, including the NICHD MFM Units Network grant. The MFM Division currently participates in the following NIH-funded studies:

-Chorhexidine Irrigation to Prevent Peripartal Infection
-Neonatal Sepsis-like Syndrome Related to *In Utero* Cytokine Exposure
-Vaginal Screening and Dental Exam
-Trial of Antibiotics vs Placebo in Bacterial Vaginosis
-Interconceptional Antibiotics to Prevent Preterm Birth
-Genital Tract Immune Factors in Pregnancy
-Beneficial Effects of Antepartum Magnesium Sulfate

4.5.2. Clinical Activities - see Section 4.1.

5. FACILITIES AND CLINICAL CAPABILITIES

The Department of Pediatrics at UAB has 84 full-time M.D. faculty including a full range of pediatric subspecialists, as well as pediatric surgical subspecialists and other medical specialists dedicated exclusively to the care of children. The Regional NICU has a state-of-the-art facility, full clinical capabilities, and experienced support staff. Full support for research is available, including an institutional research pharmacy and a respiratory therapy program. A well established multidisciplinary follow-up program with over 90% follow-up through four years of age is used to follow all extremely low birthweight infants and other infants as indicated because of medical reasons or research protocols. Special research strengths include established collaborations with reputable researchers in lung injury, ischemia and reperfusion tissue injury, infectious disorders, role of inflammatory mediators in the perinatal period, and early neurodevelopmental intervention. The GCRC at UAB has agreed to increased support of Network research. Policies and procedures developed by the Director of Division of Neonatology five years ago prioritize Network research and assure coordination of research efforts to optimize performance.

5.1. Pediatric Subspecialists

The Department of Pediatrics at UAB offers extraordinary breadth and depth in patient care, teaching, and clinical expertise and research in all pediatric subspecialty areas. The Department is under the leadership of Sergio Stagno, M.D., Professor of Pediatrics, Chairman of Pediatrics, and Physician in Chief at the Children's Hospital of Alabama. During his tenure, the Department has experienced a rapid growth in research and clinical productivity. A complete list of current full time medical faculty in the Department of Pediatrics is included in Appendix 8. There are 84 full-time M.D. faculty members in the Department of Pediatrics not including the pediatric surgeons and pediatric surgical subspecialists (18), pediatric anesthesiologists (10), pediatric radiologists (7), pediatric pathologists (4), pediatric psychiatrists (6), and pediatric psychologists (4).

The Division of Neonatology has a very special relationship and maintains active clinical research collaboration with the Division of Infectious Diseases, which is world-renowned for its work with fetal and neonatal infections, especially cytomegalovirus (Drs. Stagno and Pass), herpes virus (Dr. Whitley), and group B streptococcus (Dr. Philips). Dr. Philips, one of the neonatologists, completed this year an NICHD- funded project investigating the immunology of group B streptococcal infections in collaboration with the Division of Infectious Diseases. With NICHD support, Drs. Fowler and Pass are collecting data on sequential hearing tests on infants with congenital cytomegalovirus infection and controls to determine the epidemiology hearing deficits in cytomegalovirus infection.

The Division of Neonatology interacts closely with the five pediatric cardiologists. A portable state-of-the-art diagnostic echocardiograph is dedicated to the Regional NICU. A cardiology attending physician rounds daily in the NICU. The close relationship between neonatologists and cardiologists is mirrored in the relation of these two pediatric divisions with the

Department of Surgery. UAB is an internationally recognized center for the treatment of complex congenital cardiovascular problems and has a team of leading cardiovascular surgeons. The Regional NICU serves a vital role by providing pre- and post-operative care for infants with cardiovascular disorders, including those requiring heart transplantation.

The Division of Pediatric Neurology is actively involved in consultation and research in the Regional NICU and in the Follow-Up Program. Funduscopic examinations are performed weekly by Dr. Fred Elsas, a pediatric ophthalmologist who is principal investigator for the NEI funded Cryo-ROP Center at UAB or by Dr. Metz, another pediatric ophthalmologist. Pediatric radiologists provide the daily Radiology Conference in the Regional NICU. A strong clinical relationship has existed with the Division of Pediatric Pulmonology and its five faculty members, one of whom is also a neonatologist. There are three attending physicians in the Division of Medical Genetics. Other divisions frequently consulted are the Divisions of Pediatric Nephrology, Pediatric Endocrinology, Pediatric Hematology/Oncology, Gastroenterology/Nutrition, Pediatric Orthopedics, and Pediatric Neurosurgery. These faculty members are consultants in the Regional NICU and are frequently very involved in patient care and teaching activities in the Unit. A letter from Dr. Richard Whitley, Vice Chairman for Research, is included in Appendix 9.

Minor surgical procedures are performed by pediatric surgeons in the Regional NICU, but major procedures and surgeries, other than cardiac surgeries and Broviac catheter placement (such as laparotomy, neurosurgery, and extracorporeal membrane oxygenation), are performed at the NICU at The Children's Hospital of Alabama, which is staffed by the UAB neonatologists. This necessitates the transport of infants from the Regional NICU to the NICU at The Children's Hospital of Alabama even though the hospitals are literally side-by-side. In the past five years, 8.5% of the neonatal admissions to the Regional NICU at UAB required transfer to The Children's Hospital of Alabama. Many infants transported to the NICU of the Children's Hospital for operative procedures are transferred back to the Regional NICU. Hospitalization data collection of patients admitted to the Regional NICU is continued for those neonates that are transferred to The Children's Hospital and entered into the same data base. Since the members of the Department of Pediatrics at UAB serve as the only neonatologists at The Children's Hospital of Alabama NICU, research protocols are continued without problems despite a transfer. As UAB and The Children's Hospital share the same Institutional Review Board, continuity of all protocols is simplified following a transfer.

5.2 Description of Facilities, Equipment, and Physical Plant

The Regional NICU at UAB completed a comprehensive renovation in 1991 and a subsequent renovation in 1999. The unit now has 62 beds; 24 intensive care beds have ventilator capabilities (including an isolation room), and 38 intermediate nursery beds are used for convalescing and chronically ill infants. The Regional NICU is located adjacent to the delivery services on the same floor. Healthy neonates and those requiring observation are admitted to the adjacent Newborn Nursery (20 beds).

Square footage and electrical, gas, and other support utilities of the intensive care, intermediate care, and newborn nursery care areas conform to the latest American Academy of Pediatrics guidelines. These utilities are provided using a custom built Hill-Rom Horizon Headwall system in which all support and monitoring equipment is rack mounted. Each ventilator bed station is equipped with mountings for an infant ventilator (Infant Star), a transcutaneous PO_2/PCO_2 monitor (Novametrix), oxygen saturation monitor (Nellcor), six intravenous infusion pumps (Valleylab), and a cardio-respiratory monitor. The monitor can record two invasive blood pressures, a peripheral blood pressure, oxygen saturation, and dual temperatures. It also provides graphic and numeric trends on all variables. Each ventilator bed station is equipped with an adjustable height Air-Shields Infant Intensive Care Open Bed or an Air-Shields C100 double wall incubator. A monitor and selected equipment are mounted at each intermediate bed, as the needs of these infants are reduced. Computer terminals tied into the Hospital Information Systems mainframe are located at every other station, providing easy access to laboratory data, entering of orders, and other functions for each patient.

The NICU Conference Room has a video cassette recorder, slide projector, bookcases, and Hospital Information Systems and OBAR system computer terminals. Other areas in the Regional NICU include a room for breastfeeding, a parent room, a certified blood gas laboratory, and a chemistry micromethod laboratory. The residents' sleeping quarters, the Division's offices, and the Division library are located next to the Regional NICU.

5.3. Regional NICU Staff

The Regional NICU is under the Department of Nursing's Office of Women's Services, which is directed by Susan Scruggs, R.N., M.S.N. The remaining staff of the Regional NICU consists of the following personnel: one clinical nurse specialist, one discharge planning nurse, two lactation consultants, one unit coordinator, twelve charge nurses, 137 staff nurses, 30 patient care technicians, and 12 clerical support members. Medical care is provided by a six-member pediatric resident team (3 PL III or PL II residents, 3 PL I interns) and the three certified neonatal nurse practitioners supervised by a neonatology fellow and two neonatology attendings who rotate on a monthly basis (see Section 5.4; information on other NICU staff is included in Appendix 10).

5.4. Support Personnel, Services and Laboratories

5.4.1. Respiratory Therapy

The Regional NICU is staffed by two respiratory therapists 24 hours a day. The respiratory therapists are responsible for calibration and placement of O_2 saturation and transcutaneous O_2 and CO_2 monitors, set up and operation of ventilators and CPAP circuits, and the performance of arterial blood gas analysis. Two radiometer blood gas analyzers are located within the Regional NICU allowing instant results of blood gases, hematocrit, Na^+, K^+, Cl and ionized Ca^{++}. The respiratory therapists collaborate in research and have been instrumental in the development of the equipment and the execution of both the clinical and laboratory nitric oxide studies (Barefield et al. 1996). A designated group of NICU respiratory therapists is focused in the Network studies. These respiratory therapists assure compliance with all respiratory therapy aspects of pertinent clinical trials. Because there are at

least two respiratory therapists per shift, blinding is easily maintained throughout the hospitalization when necessary (e.g., Early INO Trial).

5.4.2. Audiology

Hearing screening is performed each weekday by a certified audiologist using a Biol-Logic Traveler LT brain stem auditory evoked potential tester.

5.4.3. Clinical Laboratories

Sophisticated laboratory capabilities are available at UAB University Hospital on a 24-hour per day, seven-day per week basis for neonates cared for in the Regional NICU. Results of the most commonly performed laboratory tests are available immediately with the use of two Radiometer analyzers located within the Regional NICU. When necessary, Regional NICU samples are run "stat," and most results are available within thirty minutes of receipt in the laboratory. All results are posted on the Hospital Information Systems computer and are immediately available to housestaff and nurses in the Regional NICU using one of many computer terminals located in the Regional NICU. A list of major hospital laboratories is in Appendix 11.

5.4.4. Imaging

Imaging services available include standard and contrast-enhanced radiographic techniques, ultrasound imaging, computerized axial tomographic scanning, nuclear medicine studies, and magnetic resonance imaging. All radiographs for Regional NICU patients are performed using a portable machine, which resides permanently in the Unit. Radiographs are kept on a viewbox in the Regional NICU Conference Room.

5.4.5. Pharmacy

The Pharmacy Department at UAB provides a pharmacist whose primary responsibility is at the Regional NICU. Services include support for total parenteral nutrition and routine performance of pharmacokinetic and peak/trough assessments in all babies receiving selected medications such as aminoglycosides and theophylline. The Regional NICU employs a unit-dose system for all medications. Collaboration between neonatologists and members of the Pharmacy Department has been closely maintained for many years in the performance of clinical trials. UAB also supports two research pharmacists, who are available 24-hours a day, 7-days a week, and whose sole responsibility is to maintain research drug supplies, blinding procedures, and documentation.

5.4.6. Other Regional NICU Staff

A biomedical engineer with full-time commitment to the Regional NICU and Newborn Nursery maintains all equipment and instrumentation. A chaplain, shared with the Obstetrics/Gynecology services, provides support to families and staff. Physical and occupational therapy support is provided by the same therapist of the Neonatal Follow-Up Program. A medical social worker is assigned to the Regional NICU and Newborn Nursery on a full-time basis.

5.4.7. Specialized Support Staff

The Division of Neonatology employs a total of 37 full-time people including eight neonatologists, six fellows, three neonatal research nurses, two research associates, two laboratory research assistants, three secretaries, one director of professional business services, two administrative associates, one data information coordinator, one data processing specialist, and eight patient account representatives (see Organizational Chart in Appendix 2). The non-M.D./R.N. personnel most important to the Neonatal Network include the data information coordinator, Deborah Hall, MRT, who has been with the Division since 1989. She extracts, records, and coordinates data in a timely and accurate fashion, freeing the research nurses for patient recruitment, and protocol adherence, and selected data abstraction. Another valuable support staff member is Cecelia Goodgame, the data processing specialist, who is responsible for entering all data into the data base in an accurate and timely manner. She has also been with the Division since 1989. She is proficient in Statistical Analysis System (SAS) and various other software applications. Ms. Goodgame analyzes data from the data base upon request. She is responsible for data entry and transmission for the NICHD Network. Ms. Goodgame and Ms. Hall are cross-trained on each other's duties for completion of data forms and data processing. All secretaries are knowledgeable in the necessary commitment to the work generated by a grant such as reports, correspondence, and any other clerical support. One of the administrative associates manages all budgets including extramural awards and office staff, and the other oversees the billing operation and clinical revenues within the Division. A description of the research nurses' training, experience, and involvement in clinical research is included in Section 7.

5.5. Clinical Capabilities

Full clinical capabilities are available for neonates at UAB. The following treatments are available at either the Regional NICU or at the NICU at The Children's Hospital: extracorporeal membrane oxygenation; high-frequency jet ventilation; high-frequency oscillatory ventilation; inhaled nitric oxide; transplant of heart, liver, and bone marrow; neonatal endoscopic surgery; and most other innovative medical and surgical therapies,

5.6. Neonatal Intensive Care Follow-Up Program

5.6.1. Evidence of an Established Neonatal Follow-Up Program

The Neonatal Intensive Care Follow-Up Program, in existence since 1977 under the direction of **Kathleen Nelson, M.D.**, provides multidisciplinary evaluations of children with selected high-risk indicators. All infants with birthweights $\leq$ 1000 g and others with abnormal neurodevelopmental evaluations are followed. Other selected high-risk neonates are followed depending on research interests and protocols. Currently, extracorporeal membrane oxygenation survivors and infants enrolled in the NICHD Early Inhaled Nitric Oxide Trial receive follow-up care. The follow-up protocol involves predischarge neurodevelopmental evaluation and six follow-up visits during the first six years of life including the required Network 18-month corrected visit. An overall follow-up rate of over 90% through age four years has been maintained during the current five-year Network cycle. This high follow-up rate has been accomplished through tracking and intensive personal contact with families.

The Follow-Up Clinic is held two half days per week in designated clinic space. A letter of commitment from Dr. Nelson to continue participation in the NICU Network is in Appendix 12.

5.6.2. Professional Staff

The multidisciplinary evaluation team includes a developmental pediatrician (Dr. K. Nelson), neonatology fellow, audiologist, two pediatric ophthalmologists, optometrist, nutritionist, two Ph.D. clinical psychologists (Dr. F. Biasini, consultant for the development of the new Bailey exam, and Dr. J. Weilenman), physical therapist, occupational therapist, social worker, and nurse coordinator. In addition, pediatric neurologists, pediatric surgeons, and other consultants are available for specific protocols. Most of the professional staff have been associated with the Follow-Up Program for more than fifteen years. These professionals hold faculty appointments within various schools at UAB. The nurse coordinator is a pediatric nurse practitioner with a Masters in Public Health degree in Maternal and Child Health; the two pediatric ophthalmologists are from the UAB School of Medicine, the optometrist is Associate Professor in the School of Optometry; the physical and occupational therapist is Assistant Professor in the College of Allied Health; the nutritionist is Professor in the Department of Nutrition/Center for Developmental Learning Disorders; the audiologist is Senior Audiologist at The Children's Hospital of Alabama; the psychologist is Associate Professor in the Department of Psychology; social work support comes from the Social Service Department of The Children's Hospital of Alabama as well as the University Hospital.

5.6.3. Neonatal Intensive Care Follow-Up Data Base

The Neonatal Intensive Care Follow-Up Program maintains a complete data base that includes pregnancy, perinatal, neonatal, and follow-up information. Neonatal information is received from the neonatal data base. Statistical analysis is performed with SAS. The Follow-Up Program and data base have been used in numerous studies on outcome of infants cared for in the nurseries at UAB including recent studies using innovative analytical techniques (Ambalavanan et al. 2000).

5.6.4. Policies and Procedures for Conducting Clinical Research

Clinical research is an essential component of the Follow-Up Program. Any project that requires follow-up is discussed with the Director of the Follow-Up Program (Dr K. Nelson). The specific evaluations required are discussed with the professional staff. The follow-up protocol is modified to meet the needs of specific studies. Because this well established program has excellent professional staff and a high follow-up rate, the data are truly representative of the targeted population, give an accurate picture of the prognosis of high-risk graduates, and are useful and dependable for research.

5.6.5. Special Developmental Disabilities Clinics

Infants with developmental disabilities are also evaluated and tested in special follow-up clinics headed by **Craig Ramey, Ph.D.** Dr. Ramey is Director of the Civitan International Research Center, an interdisciplinary research center at UAB that focuses on the prevention and amelioration of developmental disabilities and mental retardation. Dr. Ramey is a world-renowned developmental interventionist who has conducted extensive research regarding the plasticity of early development in high-risk children. Dr. Ramey directed the Infant Health and Developmental Program, a $35 million project funded jointly by the Robert Wood Johnson Foundation, the NICHD, the Bureau of Maternal and Child Health, and the Pew Charitable Trusts. Dr. Ramey is currently interested in early identification of NICU infants at high-risk for developmental delay. Dr. Ramey will be available to provide advice regarding high-risk follow-up and for design and implementation of potential developmental intervention studies. A letter of interest to participate from Dr. Ramey is in Appendix 13.

Some of the clinical research and service programs at Civitan International Research Center that provide evaluation to graduates of the Regional NICU include: Audiology Clinic, Augmentative Communication and Assertive Technology Clinic, Child Find Clinic, Child and Adolescent Behavior Clinic, Dental Clinic, Inborn Errors of Metabolism Clinic, Multiple Disabilities Clinic, Neurology Clinic, Nutrition Clinic, Optometry Clinic, Occupational Therapy Clinic, Physical Therapy Clinic, Psychoeducational Clinic, and Speech and Language Clinic. The specific functions of these clinics are included in Appendix 14.

5.6.6. Other Pediatric Clinics - Appendix 15.

5.7. Research and Administrative Strengths

A vital advantage of this proposal is the broad research and clinical collaborations that exist between members of the Division of Neonatology and other groups throughout the University and the State.

5.7.1. Research Collaborations

Interdivisional and interdepartmental cooperation has been fundamental in research growth at UAB. Research centers and other multidisciplinary groups that abound at UAB foster collaboration. Funded collaborations with over 20 established faculty members in 12 divisions, departments, and research centers throughout the University enable exceptional research (Appendix 16). The Division faculty and fellows are encouraged to work with accomplished investigators throughout the University. Research collaboration with the MFM Division (see Section 4.3.3.), Department of Pediatrics (see Section 5.3.), and the Follow-Up Program (see Section 5.6.) have been described.

A major strength at UAB is the Lister Hill Center for Health Policy at the School of Public Health. This congressionally endowed Center has a university-wide mission to facilitate the conduct of health policy research and to disseminate the findings beyond the usual channels of academic publications. Perinatal issues including prevention, health care access, financing, organization, and neonatal outcome constitute focal work areas at the Lister Hill Center. In collaboration with Janet Bronstein, Ph.D., of the Lister Hill Center and the School of Public Health, Drs. Carlo and Haywood have published on physician attitudes towards care of women in premature labor and care of the preterm infant (Haywood et al. 1994; Bronstein et al. 1995; Gardner et al. 1996; Haywood et al. 1998; Morse et al. 2000). A study to determine the effect of neonatal care on postponement of neonatal death is being completed in collaboration with Dr. Greg Alexander, Chairperson of the Department of Maternal Child Health of the School of Public Health. Other active collaborations in developmental basic and clinical research include: educational intervention in former preterm infants with Craig Ramey, Ph.D., of the Civitan Research Center; pulmonary oxidant and radical

injury with Bruce Freeman, Ph.D.; and Sadis Matalon, Ph.D., of the Division of Anesthesia Research (Cifuentes et al. 1995; Nieves et al. 1995; Tan et al. 1995); prostaglandin effects in congenital heart disease with the Department of Pathology (Faye-Petersen et al. 1995); and mechanisms of pulmonary hypertension with Suzanne Oparil, M.D., and the Department of Medicine, Division of Cardiovascular Research (DiCarlo et al. 1995; Chen et al. 1995); ureaplasma research with the Department of Microbiology (Lau et al. 1995); retinopathy of prematurity follow-up (Dr. Fred Elsas); and cytomegaloviral infection and diagnosis (Dr. R. Pass). These collaborations enhance the ability of the Division of Neonatology to excel in developmental research.

5.7.2. Clinical Collaboration with Other NICUs

The Division attendings provide neonatal care in six other NICUs in Birmingham (Section 2.3), and maintain close clinical collaboration with the three other NICUs in Birmingham (Section 2.4.). Clinical trials have been performed in collaboration with some of these NICUs. The medical directors of these NICUs have expressed interest in participation in clinical trials (Appendix 3). In addition, Dr. Carlo collects selected outcome data from all the NICUs in Alabama for the Alabama Society of Neonatology. Collaborative research is also possible through this extended external network.

5.7.3. General Clinical Research Centers Program

The General Clinical Research Centers Program (GCRC) of the Division of Research Resources at UAB provides the resources necessary for the conduct of clinical research. The primary purpose for the GCRC is to provide the clinical infrastructure to investigators who receive research funding from the other components of NIH. William B. Deal, M.D., Dean of the School of Medicine, is the principal investigator of the GCRC. The Dean has the ultimate responsibility for the administration and the operation of the GCRC and appoints the program director, associate directors, and the members of the Scientific Advisory Committee. Larry Moreland, M.D., Program Director, is responsible for the supervision, organization and operation of the GCRC. He provides a focus for the teaching of clinical research skills to housestaff, fellows, clinical associate physicians, and other junior faculty members. David Kimberlin, M.D., Associate Professor of Pediatrics (infections diseases), is Associate Program Director of the GCRC and facilitates coordination of pediatric studies. A letter of agreement to participate in the developed protocols is provided in Appendix 17.

5.8. Modification of Clinical Services in Support of Clinical Research

The Regional NICU has a long history of excellence in clinical research. All new employees are informed during the hiring process that the generation of new knowledge and the advancement of patient care through clinical research are an integral and fundamental facet of UAB's role as an academic institution. Therefore, it has not been necessary to markedly modify attitudes to accomplish clinical research. The two research nurses were experienced staff nurses in the Regional NICU before joining the research efforts of the Division. Over the years the research nurses have established strong formal and informal ties with the NICU staff which facilitate research. Policies and procedures for clinical research in the Regional NICU require that each protocol be presented to the neonatologists, NICU nurses, and other pertinent NICU personnel prior to submission to the Institutional Review Board. This process has been quite successful, as differences are resolved before the protocol is formally presented to the Institutional Review Board, expediting the process.

6. PERINATAL DATA SYSTEM

The Perinatal Data System consists of several large data resources that are readily available to the Division of Neonatology. The data resources include the Neonatology data base, the Obstetrical Automated Record (OBAR) data base, the Neonatal Intensive Care Follow-Up data base, the Hospital Information Systems data base, the Neonatology Billing data base, and the UAB NICU Network data base. Biostatistical consultation and data management resources are provided by the Department of Biostatistics located in the School of Public Health. George Howard, Ph.D., is Professor of Biostatistics and Chairman of this Department. Over 160 variables are collected for each patient admitted to the Regional NICU. The data base is used for clinical and research needs (Ambalavanan et al. 2000).

6.1. Neonatology Data Base

The Division of Neonatology's computerized data base was established in 1984 in R Base format. The purpose of this data base is to collect, tabulate, and monitor biodemographic, survival, and morbidity data in order to permit rapid identification of trends in certain neonatal problems and morbidities. The data base fields and variables are reviewed and can be updated as necessary to ensure that data is relevant and up-to-date while maintaining compatibility with previous formats. Precision and accuracy are checked by chart review and procedures internal to the computer program as well as by downloading and external analysis by other computer programs. Monthly and quarterly audits are performed on the data. Quarterly audits of entered forms are compared with hard copy logs to ensure that each infant is represented in the data base. Quality of data entry is monitored monthly with a matched print-out audit on 10% of completed charts. Abstraction audits (10%) by a review team (consisting of a physician, research nurse, and data abstractor) are performed quarterly. Additional data monitoring is performed as needed. The current data base system began in 1989 and is maintained in Statistical Analysis System (SAS). Over 160 variables are collected on each patient (Appendix 18). The primary computer used for the storage processing and analysis of data is Dell Optiplex computer with specifications of 32 MB RAM, 1.74 GB hard disk drive with a non-interlaced SVGA color monitor, and tape back-up. Data are also available on a MacIntosh Quadra 950, 16 MB with a 1GB hard disk drive and tape back-up.

The data information coordinator and data processing specialist are charged with concurrent completion of data collection upon the patient's discharge. The data information coordinator uses standardized protocols for extracting data from the medical record onto the data sheets upon a patient's discharge. The data processing specialist is responsible for data entry, quality control, data analysis, and generation of reports.

The data base is routinely used for research, administrative, and clinical care purposes. Data are extracted and analyzed quarterly to conduct internal quality assurance reviews and monitor admitting diagnoses, morbidities, practice changes, and frequency of compliance with standard screening protocols (Ballard evaluations, hearing screens, fundoscopic examinations, etc.). The neonatal data base has been used in conjunction with the OBAR system and Hospital Information System data base in an analysis of cost of care by week of gestation (St. John et al. 2000). The neonatal data base has been used also in conjunction with the follow-up data base in a comparison of neural networks versus logistic regression analysis in the prediction of neonatal outcomes (Ambalavanan et al. 2000). In-office reports can be generated daily upon request.

6.2. Obstetrical Automated Record (OBAR) Data Base - see Section 4.3.2.

6.3. Neonatal Intensive Care Follow-Up Data Base - see Section 5.6.3.

6.4. Hospital Data Base

The hospital maintains two data bases, one for financial information and one for clinical information. These data bases have existed since 1982 and at present contain over 520,000 hospital admissions and visits with up to 200 variables.

6.5. Neonatology Billing Data Base

All billing data are available through a state-of-the-art computer system that maintains a vast mainframe for the Division, the Department of Pediatrics, and many other services at UAB. Selected clinical information and demographic data as well as payment status and billing information are input into the system. In-office reports can be generated immediately upon request.

6.6. UAB Community NICU Network Data Base

The Division established this data base in 1990 for the community NICUs served by our physicians. The data base currently contains 65 variables per admission in over 3000 patients.

7. RESEARCH NURSE STAFFING

The Division of Neonatology is currently staffed with three full-time neonatal research nurses who are responsible for coordinating all clinical aspects of the Network research. Due to their experience in clinical research, including the last cycle of the NICHD Network, **Monica Collins, R.N., B.S.N., Ma.Ed.** and **Shirley Cosby, R.N., B.S.N.,** are well qualified to fulfill the responsibilities of research coordinator. They will be sharing equally the full-time position if this grant application is funded. The rest of their salary would be funded by capitation monies. If necessary, the Division has the financial resources to supplement their salary to maintain two full-time positions dedicated to the Network. A third full-time research nurse in the Division funded partially (50%) by another NIH grant, who has joined the Division, **Claire Roane, R.N., M.S.N.,** will be available as an additional research nurse to assist Ms. Collins and Ms. Cosby with Network research if necessary. Currently these three nurses split on-call hours to enroll patients in Network trials 24 hours a day as needed.

Ms. Collins and Ms. Cosby will use their combined experience of nineteen years as research nurses and ten years as staff nurses in the Regional NICU to coordinate this study. As research coordinators, Ms. Collins and Ms. Cosby will be responsible for the administrative duties of the Network studies including assisting in study implementation, staff (attending and resident physicians, nurses, and ancillary personnel) training, patient enrollment, protocol compliance, data collection, and quality assurance for data collection. In addition, they will be responsible for all Institutional Review Board correspondence. Ms. Collins and Ms. Cosby have proven to be an invaluable members of the Division research team.

Ms. Claire Roane, R.N., M.S.N., has the training and experience to aid in covering the studies. She served as a staff nurse for five years in the Regional NICU and brings to the Division additional expertise in working with the Regional NICU nurses and staff. Her position incorporates NIH funded and other extramurally funded clinical research, as well as pilot clinical studies developed by Division members. For coverage of studies, she is cross-trained by Ms. Collins and Ms. Cosby to help provide 24-hour, seven-day a week on call coverage for all inpatient studies. In order to prevent any breach of study protocol due to absence (i.e. vacation or other such event), these nurses function as a team in the responsibilities and management of research activities. Additional research nurse positions may be approved and filled with qualified individuals if needed. The Division has funded up to one additional full-time research nurse to support pilot research likely to result in extramural funding.

Currently these three full-time registered nurses provide support for all on-going clinical trials. They are responsible for assessing all patients admitted to the Regional NICU at UAB and the NICU at The Children's Hospital of Alabama for eligibility in various prospective inpatient studies. Once project eligibility is determined, informed consent is obtained and complete study procedures and data collection is initiated. The research nurse team has extensive experience in the coordination of clinical protocols.

Ms. Collins and Ms. Cosby have been coordinators of the following completed and ongoing clinical studies at UAB since 1986, listed in chronological order:

-A Prospective Randomized Controlled Trial of Early Ductus Arteriosus Ligation in Very Low Birthweight Infants.

-Infant Growth Project (NICHD)

-Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) - Phases I-III (NEI)

-Exosurf™ Neonatal

-Treatment IND Study

-Effects of Changes in Exosurf™ Pediatric Dose on A-a Gradient Improvement in Larger Infants with RDS

-Multicenter Trial of 3 vs 6 Doses of Exosurf™ Neonatal in Infants Either at Risk for or with Early Established RDS and with Birthweights >500 and < 750 grams

-Multicenter Trial of the Effects of Two Dosing Regimens of Exosurf™ Neonatal on A-a Gradient Improvement in Larger Infants with Established RDS

-Neonatal Research Network (NICHD, 1986 to 1991)
  -Generic Data Base
  -Intravenous Immunoglobulin (IVIG) to Prevent Neonatal Infections
  -Tolazoline in Persistent Pulmonary Hypertension of the Newborn
  -A Prospective Study of the Incidence and Severity of Neonatal Intracranial Hemorrhage in Infants with Birthweight 501-1500 Grams
  -Outcome and Resource Predictors for Very Low Birthweight Infants
  -Case Control Study of Contributory Factors to NEC in VLBW Neonates
  -Exosurf/Survanta Study
-Infasurf-Survanta Clinical Trial
-Effect of Rate of Advancement of Feeding on the Incidence of Necrotizing Enterocolitis in VLBW Infants
-Evaluation of Adjunctive Inhaled Nitric Oxide for the Treatment of Pulmonary Hypertension in Newborns
-Randomized, Placebo-Controlled, Dose-Response Study of Inhaled Nitric Oxide the Treatment of Persistent Pulmonary Hypertension of the Newborn
-Randomized, Placebo-Controlled Trial of Monthly RespiGam™ (RSVIG-IV) Infusions for the Reduction of the Rate of RSV Hospitalization in Premature Infants with Bronchopulmonary Dysplasia
-Multiple Dose, Placebo-Controlled, Safety and Tolerance Study of rhSOD Administered Intratracheally to Premature Neonates with RDS
-Localization of the Conus Medullaris in Preterm Infants
-Determination of Protective Levels of Maternal Antibody Against Early Onset Invasive Group B Streptococcal Disease in Neonates (NICHD)
-Pilot Study of Permissive Hypercapnia in Infants 601 to 1250 g
-A Pivotal Phase III Study of MEDI-493, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, for the Prophylaxis of Severe RSV disease in Premature Infants and Infants with Bronchopulmonary Dysplasia
-Neonatal Research Network (NICHD, 1996-Current)
  -Generic Database Study: Survey of Morbidity and Mortality in Very Low Birthweight Infants
  -*In Utero* Exposure to Magnesium Sulfate and Cerebral Palsy
  -Randomized Trial of Vitamin A Supplementation for Extremely Low Birth Weight Infants
  -Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP)
  -Randomized Trial of Minimal Ventilator Support and Early Corticosteroid Therapy to Increase Survival Without Chronic Lung Disease in Extremely Low Birthweight Infants
  -Early Inhaled Nitric Oxide Therapy in Term or Near Term Infants with Respiratory Failure
  -Randomized Controlled Trial of Parenteral Glutamine Supplementation for Extremely Low Birthweight Infants
  -Randomized Controlled Trial of Induced Hypothermia for Hypoxic-Ischemic Encephalopathy in Term Infants
  -Study to Determine if Inflammatory Cytokines are Associated with Perinatal Brain Injury and Long Term Neurodevelopmental Handicap
  -Neonatal Sepsis-like Syndrome Related to In Utero Cytokine Exposure
  -Effects of Gentle Touch and Massage on Preterm Infants – Pilot Study

Each of these studies required specific duties including anthropometric measurements, physical and gestational age assessments, serum sampling, intratracheal and intravenous medication administration, appointment scheduling, assuring parent compliance with outpatient follow-up studies, extensive data extraction from hospital medical records and retrieval of data from follow-up care providers.

Recruitment into inpatient protocols during evening, night, and weekend hours is essential for success of a multicenter trial with neonatal patients. The Division has an established record of enrollment of patients during "off hours" due to the commitment of the research nurses who manage a compensated on-call system. To maintain superior performance, the research nurses obtain consent, coordinate all procedures related to the study, and initiate the protocol 24 hours a day, 365 days per year. As in the past, it is anticipated that the Neonatal Network will require around-the-clock patient enrollment. The successful coordination of present and past clinical trials by the neonatal research nurses in the Division is evidenced by the high enrollment in all Network protocols at the UAB Clinical Center. The neonatal research nurses are extraordinarily valuable and highly skilled members of the Division of Neonatology.

8. PROPOSED PROTOCOL CONCEPT

The proposed protocol concept is a randomized controlled clinical trial to determine if a comprehensive strategy of gentle ventilation initiated soon after birth will increase survival without oxygen dependency at 36 weeks postmenstrual age (chronic lung disease, CLD) in preterm infants of 501 to 1000 g. As a management trial, a study of gentle ventilation is more difficult to do than other studies such as a placebo-controlled medication trial. A management trial is ideal for the NICHD Neonatal Network because such studies require unusual expertise in study design and implementation. In addition to the substantial evidence of the need for a trial on gentle ventilation, a main task of the NICHD Neonatal Network is to do studies that can not be performed by other groups (S. Yaffe, personal communication).

8.1. Abstract

CLD continues to be a major cause of mortality and morbidity in preterm infants. Recent data suggest that lung injury may be ventilator-induced and that the incidence and severity of CLD may be reduced with the use of a gentle ventilatory strategy. Even though small, randomized clinical trials in neonates show advantage of a gentle ventilatory strategy, the data on safety and long-term efficacy are insufficient. The objective of this proposed protocol concept is to test the hypothesis that a strategy of gentle ventilation reduces CLD or death at 36 weeks. This will be a randomized controlled trial of a comprehensive ventilatory strategy of gentle ventilation that will consist of early underwater-sealed continuous positive airway pressure (CPAP), reduced ventilator use, small tidal volumes, and permissive hypercapnia started soon after resuscitation in neonates that would receive ventilatory support and no later than one hour following intubation in infants 501 to 1000 g. The study will require a sample size of 500 infants per treatment group (1000 total). In addition to the primary outcome measure, secondary outcomes including major neonatal outcome measures (see below) and 18-month neurodevelopmental status will be assessed.

8.2. Statement of the Problem

CLD continues to be a major cause of mortality and long-term morbidity in preterm infants (Hack et al. 1995; Koumbourlis et al. 1996; Stevenson et al. 1998; Vohr et al. 2000). With the increased survival of extremely low birthweight babies (ELBW) infants and the stable or increasing incidence of CLD many more infants require long-term respiratory care in the hospital and after discharge. While etiology of CLD is likely to be multifactorial (prematurity, presence and severity of respiratory distress syndrome [RDS] and duration and intensity of oxygen supplementation and mechanical ventilation), several neonatal studies continue to identify aggressive ventilatory support as a preventable major cause of lung injury (Avery et al. 1987; Kraybill et al. 1989; Garland et al. 1995; Poets and Sens 1996; Van Marter et al. 2000). Specifically, a gentle ventilatory strategy developed at Babies Hospital of Columbia University that focuses on early use of underwater-sealed CPAP has been reported to be associated with a markedly reduced incidence of death or oxygen dependency at 28 days or 36 weeks (Avery et al. 1987; Van Marter et al. 2000). Even though these first observations were described over a decade ago and still appear to be relevant in the post-surfactant era (Van Marter et al. 2000), this ventilation strategy has not been tested in a randomized controlled trial. If proven to reduce CLD by the reported risk reduction, this would be the most effective therapy for prevention of CLD.

The proposed protocol concept intends to evaluate the impact of a comprehensive gentle ventilatory strategy consisting of early underwater-sealed CPAP, reduced ventilatory use, small tidal volumes, and permissive hypercapnia on survival without CLD defined as oxygen requirement at 36 weeks postmenstrual age in infants $\leq$ 1000 g who receive ventilatory support other than for resuscitation. Prophylactic intubation, surfactant, and mechanical ventilation are generally used in these infants if they have respiratory distress.

8.3. Hypotheses

Primary Hypothesis: A strategy of gentle ventilation in infants with birthweights 501 to 1000 g initiated soon after birth (< 1 hr) in infants who receive ventilatory support will reduce the incidence of death before 36 weeks or CLD (defined as oxygen requirement at 36 weeks, postmenstrual age by best obstetrical estimate) by a least 20% (relative risk reduction).

Secondary Hypothesis: A strategy of gentle ventilation will 1) decrease the incidence and severity (ventilator, CPAP, FiO_2) of CLD, 2) shorten hospital stay in survivors, 3) not increase other important neonatal outcome measures including intraventricular hemorrhage grades III or IV, periventricular leucomalacia, retinopathy of prematurity, nosocomial infection, necrotizing enterocolitis, and 4) increase survival without adverse neurodevelopmental outcome (cerebral palsy, hydrocephaly, microcephaly, mental retardation, blindness, or deafness) at 18 months corrected age.

8.4. Rationale/Justification

Even though there are substantial data that indicate that ventilatory management is one of the most important preventable etiologic factors in CLD, there is marked controversy about the optimal ventilatory strategies that reduce lung injury. A gentle ventilatory approach improved survival in a randomized controlled trial in adult patients. The proposed trial will address whether early implementation of a gentle ventilatory approach in preterm infants reduces CLD or death. As there is no preventive treatment with a large reduction in CLD, if proven effective, gentle ventilation could be one of the most important advances in neonatal respiratory care.

8.5. Background/Previous Studies

There is an emerging consensus that ventilator support, by itself, may inflict lung injury (Slutsky 1993; Carlo et al. 2000). Even the terms ventilator-induced lung injury (VILI) and ventilatory-associated lung injury (VALI) have been coined for this condition. Several experimental studies consistently demonstrate that markers of lung injury (pulmonary edema, epithelial injury, hyaline membranes, filtration coefficient, and lymphatic flow) are present with the use of high tidal volumes and low pressures, but not with low tidal volumes and high pressures (Dreyfuss et al. 1988; Hernandez et al. 1989; Carlton et al. 1990; Peevy et al. 1990; Dreyfuss et al. 1993; Parker et al. 1993; Carlo et al. 2000). End inspiratory volume may be the most critical determinant of lung injury (Dreyfuss et al. 1998). Lung injury is also caused by repeated collapse and reopening of the alveoli particularly if there is surfactant deficiency (Martynowiez et al. 1999; Taskar et al. 1997) and by a very low end expiratory pressure (Muscedere et al. 1994). In order to use this ventilatory approach, of smaller tidal volumes and maintenance of adequate end expiratory lung volume, tolerance of hypercapnia should be employed (ARDS Network, 2000). Relatively low levels of oxygenation can be tolerated well by neonates and may even improve pulmonary outcome (STOP-ROP Multicenter Study Group, 2000). Permissive hypercapnia is a strategy for the management of patients receiving mechanical ventilation in which priority is given to the prevention or limitation of lung injury secondary to the ventilator by tolerating relatively high levels of $PaCO_2$ rather than maintenance of normal blood gases (Carlo et al. 2000). Studies in several species have demonstrated the efficacy of permissive hypercapnia (Carlo et al. 2000). Following pilot work that demonstrated reduced mortality with a low tidal volume/hypercapnia strategy (Hickling et al. 1990), a multicenter trial of 841 adult patients with acute respiratory distress

syndrome (ARDS) revealed that low tidal volume and hypercapnia resulted in a large reduction in mortality (40 vs 31%) in the gentle ventilator group (ARDS Network, 2000). Data on permissive hypercapnia in neonates are limited. Two large retrospective studies designed to determine risk factors for lung injury in neonates concurred on the importance of ventilatory strategies as higher $PaCO_2$ values were associated with less lung injury (Garland et al. 1995; Kraybill et al. 1989). Subsequent studies at these institutions showed that $PaCO_2$ levels were no longer associated with lung injury (Young et al. 1999; Van Marter et al. 2000) presumably because hypocapnia was prevented. Two retrospective studies (Poets and Sens 1997; Van Marter et al. 2000) suggest that reduced use of ventilator support, particularly with the increased used of underwater-seal CPAP used at Columbia University, may reduce the incidence of CLD. Data from a small clinical trial suggest that the underwater seal CPAP may be a very effective technique to improve gas exchange. As the result of bubbling, infants receiving CPAP by an underwater-seal (bubble CPAP) have vibrations of their chests at frequencies similar to those of high-frequency ventilation. Minute ventilation was decreased by 39% with the underwater seal CPAP while comparable blood gas levels were maintained (Lee et al. 1998). These observations indicate that the chest vibrations produced with underwater-seal CPAP improve gas exchange when compared with the usual CPAP. In addition, meta-analyses of all the randomized controlled trials (Heicher et al. 1981, OCTAVE 1991; Pohlandt et al. 1992) of high versus low rates (and presumed low vs high tidal volumes, respectively) revealed the low tidal volume strategy lead to less air leaks and a trend for increased survival (Greenough et al. 2000).

A small pilot randomized study conducted at UAB (Mariani et al. 1999) revealed that permissive hypercapnia in infants 601 to 1250 g resulted in a marked reduction in the need for ventilatory support ($P < 0.005$). A multicenter trial of permissive hypercapnia and early postnatal steroids conducted by the NICHD Network had to be interrupted in part because of side effects of postnatal steroids. Even though the sample size was about one-sixth of the expected enrollment and hypercapnia was achieved with low ventilator rates rather than small tidal volumes, permissive hypercapnia lead to a trend for reduced CLD or death at 36 weeks (68 vs 63%) due to an effect in the 501 to 750 g infants (normocapnia 86% vs permissive hypercapnia 68%, $P < 0.05$). Furthermore, in the whole group, permissive hypercapnia reduced severity of CLD as evidenced by decreased need of ventilator support at 36 weeks from 16 to 1% ($P < 0.005$). Nonetheless, it was concluded that further trials, with more distinct ventilatory strategies, will be required to determine important effects of ventilatory strategies on CLD.

In summary, there is strong evidence that lung injury is in part due to aggressive ventilatory support and that a gentle ventilator strategy may reduce CLD in ELBW infants. If effective, this treatment could have a larger impact than other therapies used to prevent CLD (e.g., Vitamin A had a relative risk reduction of CLD or death of only 6%).

8.6. Methods/Procedure/Description of the Proposed Protocol Concept

This will be a randomized controlled trial of a comprehensive strategy of gentle ventilation consisting of early underwater-sealed CPAP, reduced ventilator use, small tidal volume, and permissive hypercapnia in neonates that receive ventilatory support other than resuscitation. Rather than prescribe an aggressive ventilatory support strategy for the control group, effort will be placed to use the current practice in the control group while infants in the experimental group will be treated with the gentle ventilation approach.

8.6.1. Randomization

Informed consent will be obtained from the parents of each infant preferably prior to birth but no later than just before ventilation is to be initiated. A code for treatment allocation will be obtained by phone-in to a central number. The code will be used to reveal the treatment allocation to the research and clinical staff only after the decision is made to intubate. Randomization will be stratified by study center and by birthweight (501-750 g and 751 to 1000 g). If the infant is randomized to the control group as described later, the clinicians will proceed with intubation and usual care. If the infant is randomized to the experimental group, CPAP will be started instead of early intubation if apnea is not present (as described in Study Intervention, Section 8.7.3.). Initiation of treatment under the protocol will start immediately after resuscitation, but no later than one hour after birth.

8.6.2 Study Population

Study criteria. Infants of either gender and any racial/ethnic groups will be eligible for enrollment if they are 501 to 1001 g, full support is intended, and mechanical ventilation is indicated clinically following resuscitation.

Exclusion criteria. Infants will be excluded from enrollment if they have a major life-threatening congenital anomaly, a permanent neuromuscular condition that affects respiration, a congenital bacterial infection, parental refusal of consent, or terminal illness (heart rate < 100 per minute, unresponsiveness to resuscitation), or a decision is made that the infant will not receive full support.

8.6.3. Study Intervention

Enrolled infants will be randomized to either a "traditional ventilation" group or a "gentle ventilation" strategy group (consisting of early underwater-seal nasal CPAP, restricted use of ventilator, small tidal volume, and permissive hypercapnia). For parental consent and clinical use the term "new ventilation strategy" will be used instead of gentle ventilation strategy to reduce the implication that this strategy may be better. Infants randomized to the gentle ventilation support group will be treated initially with underwater-sealed bubble CPAP of up to 10 cm H_2O rather than with a ventilator. If the infant has been intubated for resuscitation the switch to CPAP should occur as soon as possible after resuscitation and no later than one hour after birth. The pH will be kept ≥ 7.2 in the gentle ventilation group after one hour of life. If two consecutive blood gases more than one hour apart have a pH < 7.2, ventilation support can be increased in the gentle ventilation group. Tidal volume ≤ 5 cc/kg and relatively high ventilatory rates (≥ 60/min) will be used in the gentle ventilation group. A consistent and detailed ventilator management protocol will be developed for use in both groups. Infants in both groups will be treated with pressure-limited time cycle ventilation with or without synchronized intermittent mandatory ventilation. High frequency ventilation may be used for infants failing conventional ventilation.

Metabolic acidosis will be treated with sodium bicarbonate to keep pH > 7.20 in both groups. In both groups, PaO_2 will be kept in a comparable range (50 to 80 mm Hg or saturation of 88 to 95%). Target $PaCO_2$ in the gentle ventilation group will be >52 mm Hg whereas in the traditional ventilation support group $PaCO_2$ target will be < 48 mm Hg. These ventilatory strategies will be continued until 10 days after birth or until extubation, whichever occurs first. The same extubation and re-intubation criteria including the use of other therapies (e.g., theophylline) agreed by the Protocol Subcommittee and Steering Committee will be used for both treatment groups.

Co-interventions are common in the study population, which will consist of ELBW infants who receive ventilatory support. Randomization within centers should minimize bias which may derive from differential use of co-interventions in the gentle and traditional ventilatory strategy groups. Contamination will be minimized with the use of ventilatory management protocols, a pre-trial certification process, and prospective monitoring of center performance.

8.6.4. Definition of Primary and Secondary Outcomes

Primary outcome: The primary outcome will be death at or prior to a post menstrual age (using the best obstetrical estimate) of 36 weeks, 0 days, or CLD defined as need for supplemental oxygen ("need" defined according to the criteria being developed by Walsh-Sukys for the NICHD Neonatal Network) at a postmenstrual age (using the best obstetrical estimate) of 36 weeks, 0 days ± 1 day. FiO_2 at 36 weeks, 0 days ± 1 day will be weaned, if appropriate according to the criteria of Walsh-Sukys. The primary outcome will be assessed by comparing the proportion of infants who died or have CLD by Mantel- Henszel chi-square analysis, with center and birthweight as stratification factors.

Secondary outcome: Definitions used for the Generic Data Base and the Follow-Up Program will be used for the secondary outcomes.

8.6.5. Sample Size Estimates

Using the NICHD Neonatal Network's Generic Data Base, it is estimated that CLD/death at 36 weeks will be 0.55. Using a two-tailed type I error of 0.05, a power of 0.90 and a relative risk reduction of at least 20% (0.55 to 0.44, this is an absolute risk reduction of 11%) a sample of approximately 450 (432-450) infants per group will be needed. Assuming that in 5% of the infants there will be non-compliance, a sample size of approximately 500 per study group will be needed. To exclude a 50% increase in adverse neurodevelopment outcome at 18 months corrected age (baseline 25.5%) using a two-tailed type I error of 0.05 and a power of 0.90, the sample size would be 303 per group. Assuming a survival rate in comparable infants of 80% (Network SAVE Trial) and a follow-up rate of 78% (Vohr et al. 2000), the sample size necessary per group would be 486 infants (486 x .8 x .78 = 303). Thus a study of 500 infants per group would be sufficient for both the primary hypothesis and the neurodevelopmental outcome hypothesis.

8.6.6. Available Population in the Network/Projected Recruitment Time

Based on enrollment into similar trials by the Network (Vitamin A, SAVE), an enrollment period of 25 to 30 months is expected. In the SAVE Trial, once all 13 centers were certified, patients were enrolled at a rate of 35-40 patients per month. At this rate enrollment will require 25-30 months.

8.7. Risk/Benefits

The possible risks associated with the proposed gentle ventilation strategy are uncertain because this comprehensive treatment has not been studied in this patient population. However, each of the components of this strategy has been used in controlled trials or retrospective studies and shown to be without apparent side effects. Adverse effects of hypercapnia in retrospective studies including neurologic depression (Goldstein et al. 1990); and cerebral vasodilation, increased cerebral blood flow and intraventricular hemorrhage (Wallin et al. 1990) have not been confirmed by other retrospective studies (Levene et al. 1988; Skouteli et al. 1988; Carlo et al. 2000). Indeed, hypercapnia (average PaCO2 of 54 mmHg) has been found to be neuroprotective in experimental models (Vannucci et al. 1995). Furthermore, hypocapnia increases the risk for intraventricular hemorrhage and cerebral palsy (Graziani et al. 1992; Ikonen et al. 1992) as well as cystic periventricular leukomalacia (odds ratio of 5.4, CI 1.33-22.2) (Wiswell et al. 1996). Potential benefits of gentle ventilation include decreased CLD (Carlo et al. 2000), increased survival (ARDS Network 2000), and neuroprotection.

9. INTENT TO PARTICIPATE

As documented by the successful participation in the current cycle of this Research Network, Dr. Carlo and the other proposed investigators are well aware of and agree with the purpose and philosophy of the NICHD Cooperative Multicenter Neonatal Research Network, the process and dynamics in selecting and designing study protocols, and the paramount importance of full and unconditional participation in a multicenter study group including patient recruitment and data reporting. These investigators are fully committed to an impeccable performance in all aspects of this collaboration, as it is only through strict adherence to rigorously designed studies that optimal care, treatment, and management strategies can be best identified.

The ongoing Cooperative Multicenter Neonatal Research Network is an ideal forum to determine clinical research priorities and subsequently design, implement, analyze, interpret, and report clinical trials that investigate safety and efficacy of current and innovative treatment and management strategies. Randomized clinical trials are the archetype of clinical research in most circumstances (if applicable), as they eliminate many potential biases and bear many other advantages (McPherson 1994). However, these trials demand an enormous undertaking and much effort. The responsibilities of this task should rest on a network of selected health centers of academic and clinical excellence willing to identify priorities and design flawless studies but accept compromise on non-critical details. The Division of Neonatology at UAB presently has weekly patient discussions that facilitate implementation of research protocols through the sharing of opinions regarding controversies in treatment and management of neonatal disorders. Screening, recruitment, and protocol implementation are cornerstones in a clinical trial that when followed by accurate and complete data collection and transmission in a timely manner, are the essential components of

quality assurance that permit prompt and reliable analysis and dissemination of the results (Pullock 1994). Major problems with randomized clinical trials, such as publication bias observed even with some NIH-funded studies (Dickersin and Min 1993) and disadvantages of privately-funded research (Waldron and Cookson 1993), can be prevented with programs such as the NICHD Neonatal Network.

The investigators intend to join ongoing protocols as soon as it is feasible and, because of strategic planning over the last years, do not foresee conflicts with any of the current or planned protocols and areas of research listed in the RFA. The investigators agree to collaborate with the NICHD staff and the Steering Committee in all aspects of the grant, to receive feedback from the Advisory Board, to accept the coordinating role of the group, and to abide by the arbitration procedures. The investigators would welcome the use of objective measures designed to appraise clinical trial participation and to evaluate performance (Rosendorf LL et al. 1993) of this clinical center. Dr. Carlo will continue to closely supervise and be responsible for all aspects of this grant at UAB, to ensure that this clinical center's performance complies with and exceeds all expectations.

10. DEPARTMENT AND INSTITUTIONAL COMMITMENTS

UAB School of Medicine is a major research institution with NIH support that totaled over $129 million dollars this fiscal year. UAB ranked sixteenth in receipt of NIH grants and contracts among medical schools in the nation. University Hospital has likewise been consistently ranked as one of the best providers of health care in the nation. The Department of Pediatrics NIH support ($11.7 million) ranked seventh among pediatric departments in the country. The University Hospital and the School of Medicine have a strong reputation for excellent performance related to contracts and grants. The Deans of the School of Medicine and the School of Public Health, the University's office of grants and contracts administration, and the Chairmen of the Department of Pediatrics and Obstetrics and Gynecology have been extremely supportive of all past Network and other research efforts which have resulted in completion on a timely basis of all work in which the Division of Neonatology has been involved. The UAB organizational chart is in Appendix 19. A clinical center of the NICHD Neonatal Network at UAB will benefit from an experienced group of investigators and a clinical research team with a long-standing interest and track record of carrying out both multicenter and single center randomized clinical trials. A site visit to evaluate described facilities, equipment and systems of care can be accommodated with little or no notice.

11. ACCEPTANCE OF BUDGETARY MECHANISM

Letters from the Dean of the School of Medicine, the Chairman of the Department of Pediatrics, and the Institutional Office of Sponsored Research (Dr. Lorden) supporting capitation and the proposal in general are included in Appendix 20.

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Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants

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Objective: To determine whether the rate of feed advancement affects the incidence of necrotizing enterocolitis (NEC).

Study design: Prospective randomized controlled trial involving 185 formula-fed infants with birth weight 501 to 1500 g and gestational age ≤34 weeks. Infants were randomized into 2 groups: "slow" (n = 98), who received 15 cc/kg/d increments (a 10-day schedule to full feeds) and "fast" (n = 87), who received 35 cc/kg/d increments (a 5-day schedule to full feeds) of Similac Special Care 20 cal/oz. Feeds were increased only if well tolerated as defined by a protocol.

Results: The incidence of NEC (Bell stage ≥II) was similar in both groups (slow 13% and fast 9%, $P = .5$). The incidence of perforation (Bell stage III) was also similar in both groups (slow 4% and fast 2%, $P = .8$). Feeds were started at a comparable postnatal age in both groups (median age: slow 5 days and fast 4 days, $P = .9$). Although the neonates in the fast group attained full enteral intake earlier (median days [25th and 75th percentiles]: slow 15 [12, 21] and fast 11 [8, 15], $P < .001$) and regained their birth weight earlier (slow 15 [11, 20] and fast 12 [8, 15], $P < .05$), their ages at discharge were not statistically different (slow 47 [31, 67] and fast 43 [29, 62], $P = .3$)

Conclusions: A greater than twofold difference in the rate of feed advancement from 15 cc/kg/d to 35 cc/kg/d did not affect the incidence of NEC ≥ stage II. Factors other than feed advancement appear to be more important in the pathogenesis or progression of NEC. (J Pediatr 1999;134:293-7)

Necrotizing enterocolitis is a major cause of mortality and morbidity in preterm infants. The incidence of NEC in the National Institute of Child Health and Development Neonatal Research Network has been 8% to 10% of very low birth weight infants, with center differences in incidence from 3.9% to 22.4%.[1,2] The cause of NEC is inadequately understood, although many factors such as enteral feeds, hypoxia, ischemia, patent ductus arteriosus, and infection have been associated with an increased incidence of NEC.[3-5] Several retrospective studies suggest that rapid advancement in feeds may be associated with an increased incidence of NEC.[6-8] A case control study by the National Institute of Child Health and Development Neonatal Research Network of 249 neonates with NEC revealed that the infants who had NEC received significantly more enteral nutrition in the 3 days before the diagnosis of NEC compared with a control group.[9] In that study the incidence of NEC in individual centers ranged from 2% to 19%, and 2 centers accounted for 63% of the cases.[9] During that time period the 16% incidence of NEC in our center was the second highest of the 8 clinical centers. At that time VLBW neonates frequently achieved full enteral intake in <5 days after initiation of feeds. The purpose of this study was to determine whether the rate of advancement of feeds influenced the incidence of NEC. We tested the hypotheses that in VLBW neonates: (1) slow feed advancement (15 cc/kg/d) decreases the overall incidence of NEC (Bell stage ≥ II) compared with fast feed advance-

NEC Necrotizing enterocolitis
PDA Patent ductus arteriosus
VLBW Very low birth weight

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Presented in part at the Pediatric Academic Societies Meeting, Washington, DC, May 2-6, 1997.
Submitted for publication Aug 5, 1998; revision received Nov 4, 1998; accepted Dec 2, 1998.

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0022-3476/99/$8.00 + 0 9/21/96310

Table I. Incidence of NEC (≥stage II) by weight subgroups

Birth weight (g) stratum	Slow NEC/Total (%)	Fast NEC/Total (%)	P value
501-750	2/13 (15)	0/9 (0)	NS
751-1000	7/30 (23)	3/24 (13)	NS
1001-1250	3/22 (13)	4/25 (16)	NS
1251-1500	1/33 (3)	1/29 (3)	NS
Total	13/98 (13)	8/87 (9)	NS

ment (35 cc/kg/d) and (2) slow feed advancement decreases the incidence of NEC with intestinal perforation (Bell stage III) compared with fast feed advancement.

METHODS

Subjects

From January 24, 1994, until December 30, 1996, 187 infants with birth weight 501 to 1500 g and gestational age ≤34 weeks admitted to the regional neonatal intensive care unit at the University of Alabama at Birmingham were prospectively enrolled in the trial. The exclusion criteria included (1) Apgar score <3 at 5 minutes, (2) hemodynamic instability requiring pressors to maintain blood pressure at the time of initiation of feeds, (3) presence of cyanotic congenital heart disease or other major malformation, (4) polycythemia (venous hematocrit >70%), (5) partial or double volume exchange transfusion before initiation of feeds, (6) human milk feeds (partial or total), and (7) multiple gestation of triplets or more. Small for gestational age infants, large for gestational age infants, infants undergoing mechanical ventilation, and infants who received indomethacin were not excluded. Trophic (minimal enteral) feeds were not used. Eligibility was assessed after the decision to initiate feeding was made by the clinical team. Informed parental consent was obtained. Randomization was performed according to weight stratification into 4 groups: 501 to 750 g, 751 to 1000 g, 1001 to 1250 g, and 1251 to 1500 g. Shuffled blocks of 2, 4, and 6 sealed envelopes for each weight group were used. The person obtaining parental consent was masked to the odds of a subsequent infant receiving either treatment. Twins were randomized to the same treatment mode according to randomization of the first eligible of the pair.

Protocol

The protocol was approved by the institutional review board before the trial was begun. The patients were randomized into 2 groups: (1) "slow" feeding group: feeds were started at 20 cc/kg/d and advanced by increments of 15 cc/kg/d to a maximum of 160 cc/kg/d (a 10-day schedule to full feeds), (2) "fast" feeding group: feeds started at 35 cc/kg/d and advanced by increments of 35 cc/kg/d to a maximum of 160 cc/kg/d (a 5-day schedule to full feeds). Both groups started feeds with Similac Special Care 20 cal/oz formula and were switched to Similac Special Care 24 cal/oz formula when full feeds were reached. Oral medications were not given until full enteral feeds were attained.

The patients were fed every 3 hours with an orogastric tube. Aspirates (residuals) from the orogastric tube were checked before every feed. If aspirates were ≤20% of total feed and the abdominal examination was normal, feeds were advanced according to the protocol. If aspirates were between 20% and 30% and the abdominal examination was normal, feeds were continued, but no increase in feeds was done on that day. Feeds were temporarily discontinued for 24 hours and then continued at half the previous volume for aspirates between 30% and 40%. If the aspirates were ≥40% or the abdominal examination was abnormal regardless of the aspirates, a complete blood count and an abdominal radiograph were obtained. If both investigations were normal, feeds were temporarily discontinued for 24 hours and then resumed at half the previous volume and advanced at the previous day's rate. An abnormal abdominal examination was defined as 1 or more of the following: (1) abdominal distention, (2) erythema of the abdominal wall, (3) abdominal tenderness, (4) decreased bowel sounds, (5) increased abdominal girth, and (6) gross or occult blood in the stools.

NEC was defined according to the Bell stages.[10] Bell stage II (proven NEC) includes radiographic findings of pneumatosis intestinalis or portal vein gas with clinical signs including poor feeding, increased residuals, or abdominal distention with bloody stools. Bell stage III includes radiographic observation of pneumoperitoneum with the previously described clinical signs associated with deterioration of vital signs and septic shock.

Presence of a PDA, when suspected on clinical evaluation, was confirmed by echocardiography. Indomethacin was administered at standard doses (0.2 mg/kg per dose, 3 doses at 12-hour intervals). There was no change in the feeding schedule in the presence of a PDA.

The end point of the study was when the patient was discharged or had NEC (stage ≥ II) before discharge home. The results were analyzed by intention to treat.

Statistics

The expected incidence of NEC (≥ stage II) in the fast feeding group was 16% based on the incidence at our center, and the anticipated incidence of NEC in the slow feeding group was estimated to be 5% based on the incidence at the centers with slower feed-

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ing protocols.[9] The sample size was estimated at a total of 185 with the Fisher-Irwin tables for sample size estimation with power of 80%, α of 0.05, and a small excess to compensate for small variations in the actual incidences from the expected incidences. Chi-squared analysis, *t* test, or Wilcoxon rank sum test was used for statistical analysis of the data, depending on whether the data were normally distributed. A P value < .05 was considered statistically significant.

RESULTS

During the enrollment period 605 neonates with birth weight 501 to 1500 g were admitted to the neonatal intensive care unit. A total of 295 patients were excluded because of 1 or more of the following reasons: human milk feeds (n = 153), major malformations (n = 71), died before initiation of feeds (n = 54), fed before consent was obtained (n = 32), low Apgar scores (n = 26), congenital heart disease (n = 22), transferred to another hospital before initiation of feeds (n = 4), triplets or quintuplets (3 sets), unable to get consent because of maternal illness (n = 4), and transpyloric feeds (n = 3). Parents of 310 neonates were approached, and randomization was performed after informed consent was obtained on 185 infants (rate of 60%).

There were 7 protocol violations including patients fed human milk at parent's request (n = 3), patient transferred to another hospital before receiving full feeds (n = 2), and infants with multiple episodes of feeding intolerance taken off the study at the request of the attending physician (n = 2). Data on these infants were included in the analysis, because analysis was done on the basis of intention to treat. The data from 185 infants (slow 98, fast 87) were analyzed. Birth weight, gestational age, sex, and race were comparable in the 2 groups (Table I). Feedings were started at a comparable postnatal age in both groups (slow 5 days, fast 4 days, P = .9).

Table II. Postnatal age in relation to nutrition and discharge

	Slow	Fast
Age at starting feeds (d)	5 (3-7)	4 (3-7)
Age at full feeds (d)	15 (12-21)	11 (8-15)*
Age when birth weight regained (d)	15 (11-20)	12 (8-15)*
Age at discharge (d)	47 (31-67)	43 (29-62)

Data are shown as median days (25th to 75th percentiles).
*P < .05.

No difference was seen in the incidence of NEC (Bell stage ≥ II) between both groups (slow 13%, fast 9%, P = .50) or for each of the weight subgroups (Table I). It should be noted that although subgroup analysis by weight is shown, the small sample size of each stratum makes type II error more likely. The incidence of intestinal perforation (Bell stage III) was also comparable in both groups (slow 4%, fast 2%, P = .8). No significant difference was seen in mortality resulting from NEC (in entire feeding group: slow 2%, fast 3%, P = .9 and in those who had NEC stage ≥ II: slow 2 of 13, fast 3 of 8, P = .32 by Fisher's Exact test). The babies in the fast group had NEC at the age of 25 ± 14 days (mean ± SD), whereas the neonates in the slow group had NEC at 18 ± 9 days (P = .3). The average volume of feeds in the 3 days before NEC in the fast group was 122 ± 44 cc/kg/d (mean ± SD) and 96 ± 40 cc/kg/d in the slow group (P = .07). In the 3 days before the onset of NEC, no difference was noted in feeding intolerance (<15% of neonates in either group with more than 20% residuals).

The incidence of NEC in the neonates enrolled in this trial (combined) was not significantly different from the incidence seen historically in the same unit (fast + slow 11% vs historical 16%, P = .4). Although not part of the trial, the incidence of NEC in the neonates excluded because of human milk feeding was 7% (fast + slow 11% vs human milk 7%, P = .4).

The age at which the diagnosis of NEC was made was similar in the 2 groups. Three infants in each group had NEC before reaching full feeds. No contribution by the epidemic form of NEC was noted, because there were never more than 2 cases of NEC (Bell stage ≥ II) per month (in both groups combined) during the study.

Data on postnatal age were not normally distributed and are reported as median with the 25th and 75th percentile (Table II). As expected, a significant difference was seen between the 2 groups in postnatal age at full feeds (slow 15 days [12 to 21], fast 11 days [8 to 15]; P < .001) and the postnatal age to regain birth weight (slow 15 days [10 to 20], fast 12 days [8 to 15]; P < .05). When the number of days to achieve full feeds from initiation of feeds were compared, 46 (47%) achieved full feeds in 10 days in the "slow" group, and 49 (56%) achieved full feeds in 5 days in the fast group. However, the age at discharge was not statistically different (slow 47 days [31 to 67], fast 43 days [29 to 62], P = .3).

The 2 groups were comparable in variables that may influence the incidence of NEC such as antenatal steroid exposure, postnatal indomethacin use (either as prophylaxis for intraventricular hemorrhage or as management of PDA), the presence of symptomatic PDA (all given indomethacin), and the placement of umbilical arterial catheter.

The demographics of the VLBW neonates who were enrolled for this study were comparable to those of the total VLBW population admitted to

the nursery at that time period (mean birth weight 1045 g, 28 weeks' gestation, 49% male). The incidence of NEC in the VLBW neonates not enrolled in the study (9.5%) was also similar to the incidence of NEC in the study (11%). The median length of hospital stay was also similar in the babies who did not participate in the study (49 days) compared to those who participated in the study (45 days).

DISCUSSION

The incidence of NEC (Bell stage ≥II) and NEC with intestinal perforation (Bell stage III) did not change with more than a twofold difference in the rate of feed advancement. Also, the timing of the development of NEC did not differ between both groups. Although the birth weight was regained earlier in the fast group, this did not translate into an earlier discharge. The fast group reached full feeds earlier, which indicates that this rate of feed advancement is equally tolerated compared to the slow feeding regimen.

Although the study was a randomized controlled trial, it had some important limitations. It could not have been done in a masked manner. To decrease the influence of potential bias, feed intolerance was defined by strict criteria, and a radiologist independent of the study made the radiologic diagnosis of NEC. A different number of patients were noted to have been randomized to each group (slow 98, fast 87). Other than the effect of chance in the technique of block randomization, 1 factor that had an effect is the number of twins randomized to each group. Five sets of twins were randomized to the slow group, and 4 were randomized to the fast group. Another limitation is that although the sample size was calculated on a projected incidence of NEC at 16% in 1 group and 5% in the other group based on past studies, the actual incidences were lower (slow 13%, fast 9%). However, the post-hoc power of the study indicating the groups were similar was 87%, and although a type II error is still possible, it is less likely (a sample size of 1850 is required to show that the difference in the incidence of NEC noted between the groups is statistically significant at a .05 and 80% power).

The effect of feeding schedules on the incidence of NEC has been widely debated. In support of our observations 2 prospective randomized trials demonstrated no increase in the incidence of NEC when feed increments were increased. Book et al[11] compared 2 feed increments, 10 cc/kg/d and 20 cc/kg/d. No significant difference was seen in the incidence of NEC between the 2 groups. However, the sample size was small (total n = 29), and a type II error was possible. A recent prospective randomized study by Caple et al[12] showed no difference in the incidence of NEC between feed advancements of 20 cc/kg/d and 30 cc/kg/d. These results are consistent with our study, because we did not detect any increase in the incidence of NEC even with a wider range of feeding advancements of 15 cc/kg/d and 35 cc/kg/d. On the other hand, several retrospective case control studies suggest that aggressive increments in feeds may increase the incidence of NEC. Anderson and Kliegman[7] showed that infants who had NEC compared with a matched control group had significantly larger feeding increments. Similar results were obtained in other retrospective case control studies by Covert et al[6] and McKeown et al.[8] When compared with a matched control group, the infants with NEC were fed earlier and received larger feeding volumes.[8] These retrospective case control studies reveal results that may not be comparable with ours. There may be 2 reasons for this: (1) in some cases feed increments were greater than 35 cc/kg/d, and (2) the neonates with the NEC group were found to have started feeds earlier than the control group. In our study both groups started feeds at a similar postnatal age.

Four chart review studies revealed an association between the incidence of NEC and rapid feeding practices. Krouskop[13] reported that more than 50% of infants who had NEC had received aggressive feeding increments. Book et al[11] noted dramatic increases in the incidence of NEC when feeding protocols became faster. In a similar manner, Spritzer et al[14] found dramatic decreases in the incidence of NEC in their neonatal care unit after introducing a slower feeding regimen. Finally, Goldman,[15] in another chart review, found that patients who had NEC had larger feeding increments before the episode of NEC occurred. These studies have results that contradict our prospective randomized study. Chart review studies have the limitations common to other forms of retrospective studies. No control of other variables may influence the incidence of NEC. On the other hand, known and unknown confounders are likely to be equally distributed between groups in a randomized trial such as this study.

This study has shown that feed increments of 35 cc/kg/d compared with 15 cc/kg/d were equally well tolerated and did not increase the incidence of NEC in VLBW neonates matched for weight and gestational age. Therefore factors other than the rate of feed advancement may be more important in the pathogenesis or progression of NEC. However, it does not follow that increments larger than 35 cc/kg/d are equally safe in the VLBW population. It is possible that larger increments, beyond a currently undefined value, may in fact alter the risk of NEC. Marked intercenter differences in the incidence of NEC[2,15] indicate that further investigation of the determinants of NEC should include analysis of variations in clinical practice and sociodemographic variables in addition to the variables of prematurity, infection, hypoxia, ischemia, and feeding practices that are commonly implicated.

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Randomized Trial of Permissive Hypercapnia in Preterm Infants

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ABSTRACT. *Objective.* To determine whether a ventilatory strategy of permissive hypercapnia (PHC) reduces the duration of assisted ventilation in surfactant-treated neonates weighing 601 to 1250 g at birth.

Design. Forty-nine surfactant-treated preterm infants (birth weight: 854 ± 163 g; gestational age: 26 ± 1.4 weeks) receiving assisted ventilation were randomized during the first 24 hours of age to a PHC group ($Paco_2$: 45–55 mm Hg) or to a normocapnia group (NC; $Paco_2$: 35–45 mm Hg). The primary outcome measure was the total number of days on assisted ventilation. Uniform extubation and reintubation criteria were used for both groups. All patients received aminophylline before extubation.

Results. The total number of days on assisted ventilation expressed as median (25th–75th percentiles) was 2.5 (1.5–11.5) in the PHC group and 9.5 (2.0–22.5) in the NC group (Mann-Whitney *U* test). The number of patients on assisted ventilation throughout the first 96 hours after randomization was lower in the PHC group (log rank test). During that period, the ventilated patients in the PHC group had a higher $Paco_2$ and lower peak inspiratory pressure, mean airway pressure, and ventilator rate than did those in the NC group. The percentage of patients requiring reintubation within 24 hours postextubation (PHC 17% vs NC 28%) and supplemental oxygen at 28 days of life (PHC 43% vs NC 64%) and the total days of oxygen supplementation (PHC 15 [4–53] vs NC 32 [17–50]) did not differ between the groups. There were no differences in mortality, air leaks, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, or patent ductus arteriosus.

Conclusion. A ventilatory strategy of PHC in preterm infants who receive assisted ventilation is feasible, seems safe, and may reduce the duration of assisted ventilation. *Pediatrics* 1999;104:1082–1088; *assisted ventilation, respiratory distress syndrome, gentle ventilation, lung injury.*

ABBREVIATIONS. BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; PHC, permissive hypercapnia; RDS, respiratory distress syndrome; NC, normocapnia.

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This work was presented at the Annual Meeting of the Society of Pediatric Research, Pediatric Academic Society; May 2–6, 1997; Washington, DC.
Received for publication Jun 30, 1998; accepted Mar 2, 1999.

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Despite important advances in respiratory care, lung injury is still a leading cause of neonatal morbidity in neonates who receive ventilatory support. Although surfactant administration in neonates is very effective, it has not decreased the incidence of bronchopulmonary dysplasia/chronic lung disease (BPD/CLD).[1,2] The duration and intensity of assisted ventilation may be important determinants in the development of lung injury. Large tidal volumes are considered particularly harmful to the developing lung.[3] Retrospective studies suggest that ventilatory strategies that lead to relative hypocapnia during the first days after birth may increase BPD/CLD.[4,5] Permissive hypercapnia (PHC) is a strategy for the management of patients receiving assisted ventilation in which relatively high levels of $Paco_2$ are accepted to avoid high tidal volumes, pulmonary overdistention, and hypocapnia, thus potentially reducing lung injury.[6,7] PHC has been reported to be a safe alternative to conventional normocapnic assisted ventilation in adult patients with acute respiratory distress syndrome[8–10] and may increase survival.[11] PHC may be important in the management of preterm infants with respiratory distress syndrome (RDS).[12] Data on hypercapnia in ventilated neonates are limited, and none of the reported studies predetermined or controlled the degree of hypercapnia. We performed a randomized, controlled pilot study to evaluate whether a strategy of PHC, initiated during the first 24 hours after birth in neonates weighing 601 to 1250 g at birth, decreases the number of days of assisted ventilation.

METHODS

Study Outcomes

The primary hypothesis was that a ventilatory strategy of PHC would reduce the number of days on assisted ventilation by 35%, compared with a normocapnic approach. The primary outcome measure was the total number of days on assisted ventilation. The secondary outcome measures included the total number of days on supplemental oxygen, the incidence of BPD/CLD, postnatal steroid administration, air leaks, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, patent ductus arteriosus, necrotizing enterocolitis (≥stage II-A), and length of hospitalization.

Eligibility and Randomization

This study was conducted in the Regional Newborn Intensive Care Unit at the University of Alabama at Birmingham between November 1, 1995 and December 9, 1996. The study protocol and informed consent form were approved by the institutional review board.

Infants were eligible for the study if all the following criteria were met: 1) birth weight of 601 to 1250 g; 2) surfactant-treated RDS on assisted ventilation; 3) postnatal age <24 hours; and 4)

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written parental informed consent. Infants were excluded for any of the following reasons: 1) 5-minute Apgar score <3; 2) small for gestational age; 3) congenital anomalies or suspected congenital infection; 4) multiple pregnancy of triplets or more; and 5) infant not expected to need prolonged ventilatory assistance as judged by the attending neonatologist. The patients were assigned to either a PHC or a normocapnia (NC) group using a permuted block randomization procedure consisting of a random sequence of blocks of 4, 6, 8, and 10. The group assignments were recorded and sealed within sequentially numbered opaque envelopes. The odds of assignment to one of the two groups were not known to the investigators. To ensure a similar birth weight mix, infants were stratified into the following groups: 601 to 750 g, 751 to 1000 g, and 1001 to 1250 g. Twins who met enrollment criteria were randomized to the same group according to the randomization of the first eligible infant of the pair.

Ventilator Management

All infants received initial assisted ventilation with an Infant Star ventilator (Infrasonics, Inc, San Diego, CA), a time-cycled pressure-limited ventilator. High frequency ventilation was used at the discretion of the attending physician. Oxygenation was monitored continuously with a pulse oximeter. Ventilatory management was the responsibility of the attending physicians, but different algorithms were provided for infants randomized to each treatment group. The goals for pH and $Paco_2$ were different in the two groups of infants. In the NC group, the goals were to keep $Paco_2$ between 35 and 45 mm Hg and pH ≥7.25. In the PHC group, ventilatory management was directed to maintain $Paco_2$ between 45 and 55 mm Hg and pH ≥7.20. These goals were used for the first 96 hours after randomization. After that time, the changes in the ventilator settings were directed at the pH criteria, allowing high levels of $Paco_2$ also in the NC group. The goal for Pao_2 level was between 50 and 80 mm Hg in both groups.

To achieve these goals, ventilator setting changes followed a modified clinical algorithm, developed for the management of pressure-limited ventilation in infants with RDS.[13] The algorithm incorporates accepted concepts of the effects of neonatal assisted ventilation on gas exchange. Briefly, CO_2 elimination was enhanced by increasing the ventilatory frequency. If this failed, peak inspiratory pressure was increased. During the weaning process, priority was given to reduce peak inspiratory pressure. Oxygenation was improved predominantly by increases in mean airway pressure when the FIO_2 was >0.70. This was accomplished by increasing positive end expiratory pressure or inspiratory time. If hypoxemia was persistent, peak inspiratory pressure was increased. If FIO_2 was <0.40, increases in oxygen concentration were performed for hypoxemia. When the FIO_2 was between 0.40 and 0.70, the parameter modified was decided based on the level of mean airway pressure and chest excursion. Although the algorithm was based on arterial blood gas measurements, clinical assessment, including, but not limited to, chest wall movements, breath sounds, and cardiovascular function, was performed simultaneously. The algorithm suggested the type of ventilator setting change but not its magnitude, which was decided on clinical grounds.

Objective criteria were used for extubation to minimize bias. Infants were extubated from assisted ventilation if all the following criteria were met: peak inspiratory pressure ≤19 cm H_2O, ventilator rate ≤10 per minute, FIO_2 ≤0.4, and arterial pH ≥7.25. An aminophylline loading dose was given before extubation. Continuous positive airway pressure was used as clinically indicated. Reintubation was performed for a pH <7.20, respiratory failure, or severe apneic episodes needing assisted ventilation according to the attending physician. The defined extubation criteria were followed for every period on assisted ventilation, except when patients required more than one reintubation for apnea. In these patients, a new extubation was attempted 5 to 7 days after the previous failure. Patients were weaned from oxygen supplementation when they were able to maintain oxygen saturation ≥90% while breathing air.

General Care

At least one dose of surfactant (Survanta, Ross Laboratories, Columbus, OH) was administered before randomization. Repeated doses were given if the FIO_2 was >0.3 and/or if the mean airway pressure was >7 cm H_2O. Dexamethasone was considered for infants who were ventilator-dependent at 10 days of age, if they had radiologic findings consistent with developing chronic lung injury in the absence of confounding circumstances, such as patent ductus arteriosus, pneumonia, or sepsis. A 7-day course of dexamethasone at 0.6 mg/kg per day was used. A second, tapering 9-day course (0.6, 0.4, and 0.2 mg/kg per day for 3 days each) was given as clinically indicated.

Intravenous fluids were started at 130 to 200 mL/kg per day in infants ≤750 g, and at 100 to 150 mL/kg per day in infants between 751 and 1250 g. The total fluid intake was adjusted as needed, based on urinary output, weight change, and serum sodium values. All patients received indomethacin for intraventricular hemorrhage prophylaxis (a daily dose of 0.1 mg/kg for 3 days). Sodium bicarbonate was given for serum bicarbonate ≤ 16 mEq/L.

Data Collection and Definitions

Maternal demographics and obstetric history of pregnancy, labor, and delivery were obtained from the mother's medical record. Gestational age was assessed by the best obstetrical estimate and the Ballard examination of the neonate. Infants whose birth weight was below two standard deviations were considered small for gestational age.[14] An initial cranial ultrasound was performed before study entry. Subsequent studies were performed routinely on days 5 through 7 and 28 ± 7 or when clinically indicated. The arterial blood gas values were recorded before randomization and closest to 6, 12, 24, 36, 48, 60, 72, 84, and 96 hours postrandomization while the infant received assisted ventilation. The corresponding ventilator settings at these times were recorded. Data were collected at prospectively scheduled times and recorded on standardized forms.

The total duration of assisted ventilation was calculated from the sum of all periods of assisted ventilation until final extubation. Time on continuous positive airway pressure was not counted as assisted ventilation. The total duration of oxygen supplementation was calculated from the sum of all periods of any technique of oxygen supplementation, including after transfer or discharge. BPD was defined as oxygen requirement and abnormal chest radiograph on day 28 of postnatal age, with oxygen requirement for at least 21 of the first 28 days.[15] Air leaks included pneumothorax and/or pulmonary interstitial emphysema. The severity of intraventricular hemorrhage was graded according to the criteria of Papile et al.[16] A hemorrhage was considered to have progressed if: 1) a new intraventricular hemorrhage developed from an initial negative head ultrasound; 2) there was a progression in any grade of intraventricular hemorrhage; or 3) a second intraventricular hemorrhage was noted in the hemisphere opposite from the existing hemorrhage. A diagnosis of periventricular leukomalacia was made if the cranial ultrasound showed postnatal development of multiple cystic echolucencies in the cerebral white matter. Proven sepsis was defined as a positive blood culture result for bacteria or fungus treated by the clinicians at any time during hospitalization. The presence of patent ductus arteriosus was confirmed by echocardiography. Modified Bell's criteria were used for necrotizing enterocolitis staging.

Sample Size Determination and Statistical Methods

At the time when the study was designed, the mean number of days on assisted ventilation for infants weighing 601 to 1250 g in our unit was 14 days. Using an estimated standard deviation of 6 days, a sample size of 24 infants per group would be required to detect a 5-day difference (a reduction of 35%) in days on assisted ventilation between the groups with a power of 0.80 and a type I error of 0.05 (two-tailed). The analysis was performed according to intention to treat, and crossover was not allowed. Results were analyzed by the Student's t test, χ^2, or Fisher's exact test, as appropriate for parametric data and by Mann-Whitney U rank sum test for nonparametric data. A Kaplan-Meier analysis was performed, comparing the time on assisted ventilation during the first 96 hours after randomization and throughout the hospital stay in the two groups. A P value <0.05 was considered to be statistically significant.

RESULTS

During the enrollment period, a total of 171 preterm infants weighing 601 to 1250 g at birth were

born at the University of Alabama at Birmingham (Fig 1). Of these infants, 57 did not receive assisted ventilation in the first 24 hours after birth; thus, 114 infants were potentially eligible. A total of 65 neonates were excluded for the following reasons: Apgar score <3 at 5 minutes (n = 7); small for gestational age (n = 5); congenital anomalies/infection (n = 11); triplet (n = 1); not expected to need prolonged mechanical ventilation (n = 24); consent denied (n = 12); or the attending physician's decision not to randomize based on evidence of pulmonary hypertension or early pulmonary interstitial emphysema (n = 5). Of the infants, 49 were randomly assigned, 24 to the PHC group and 25 to the NC group. All patients had radiographs consistent with RDS. Birth weight, gestational age, gender, race, prenatal steroid administration, maternal chorioamnionitis, percentage of cesarean section, postnatal age at study entry, Apgar scores, and prerandomization arterial blood gases and oxygenation indexes did not differ significantly between the two groups (Table 1). In addition, the degree and need for resuscitation, the overall delivery room management, and time to intubation did not differ between the groups.

Respiratory Outcomes

The duration of assisted ventilation was not reduced significantly in the PHC group (Table 2). Because the results were not distributed normally, the median and the 25th–75th percentiles are used to express these values. The total number of days on assisted ventilation was 2.5 (1.5–11.5) in the PHC group and 9.5 (2.0–22.5) in the NC group (P = .17; Mann-Whitney U test). However, the number of patients on assisted ventilation during the 96 hours after randomization was lower ($P < .005$; log rank test) in the PHC group (Fig 2).

During the first 96 hours after randomization, the ventilated patients in the PHC group had higher ($P < .05$) $Paco_2$ values (Fig 3) and lower peak inspiratory pressures, mean airway pressures, and ventilator rates than did those in the NC group at most 12 hour intervals after randomization (Fig 4); impairment of oxygenation, reflected by arterial to alveolar oxygen ratio and FIo_2, was comparable in the two groups (Fig 5).

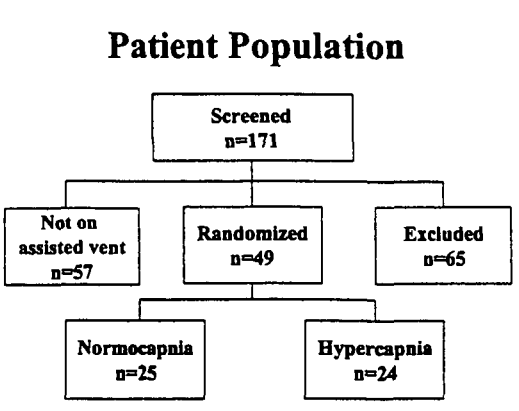

Fig 1. Trial profile summarizing participant screening and randomization. The primary reason for exclusion was no need for assisted ventilation or not expected to need prolonged ventilation.

The total duration of oxygen supplementation, the incidence of BPD, oxygen requirement at 36 weeks, air leaks, reintubations, and the use of postnatal steroids and postextubation continuous positive airway pressure did not differ significantly between the two groups (Table 2). The rate of reintubation within 24 hours postextubation was 17% in the PHC group and 28% in the NC group (not significant). The mean peak inspiratory pressure before extubation was 15 cm H_2O in the PHC group and 16 cm H_2O in the NC group (not significant). Of the survivors in the PHC group, 67% (14/21) required at least one reintubation at some point during their hospitalization (7 for respiratory failure, 5 for apnea, 1 for necrotizing enterocolitis, and 1 for ventriculo-peritoneal shunt placement). Of the survivors in the NC group, 55% (12/22) were reintubated (8 for respiratory failure, 3 for apnea, and 1 for necrotizing enterocolitis). Only 2 infants (both randomized to the NC group) received high-frequency ventilation at any time during the hospitalization.

Nonrespiratory Outcomes

Three patients in each group died. The causes of death in the PHC group were grade 4 intraventricular hemorrhage in 2 patients and necrotizing enterocolitis/sepsis in 1 patient. In the NC group, 2 patients died from grade 4 intraventricular hemorrhage and 1 died because of respiratory failure. There were no significant differences in any of the nonrespiratory outcome measures between the two groups (Table 3). Three patients (all in the PHC group) did not have a head ultrasound performed before randomization.

DISCUSSION

Assisted ventilation in infants with RDS has resulted in improved neonatal survival.[17] However, its excessive or prolonged use has been associated with an increased incidence of BPD/CLD.[18-20] In this pilot study, we found that a ventilatory strategy of PHC for the management of preterm infants on assisted ventilation is feasible and not associated with an increased rate of complications, compared with a traditional normocapnic approach. The duration of assisted ventilation was decreased in the first 96 hours after randomization in the PHC group, but the total duration of assisted ventilation in the PHC group did not decrease significantly.

Our study has some limitations that preclude firm conclusions. The failure to attain a level of statistical significance in the total duration of assisted ventilation may be primarily attributable to the marked variability in duration of ventilation and a small sample size, with the possibility of a type II error, because the power of the test was below the desired power of 0.80. The variability in the duration of ventilation was in part because a ventilatory strategy of PHC may not necessarily decrease the need for assisted ventilation in infants with apnea or other nonrespiratory causes. A choice of ranges of $Paco_2$ that separated the groups more may have led to larger differences in the duration of ventilation. Because this study could not have been masked, to decrease the influence of any potential bias on dura-

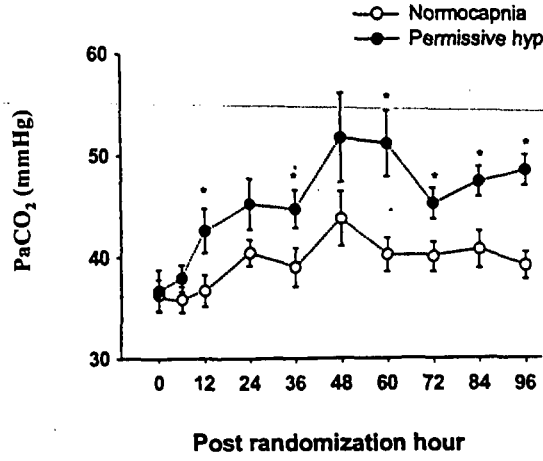

Fig 3. $Paco_2$ levels (mean ± standard error of the mean) in both groups during the first 96 hours after randomization. $Paco_2$ values were higher in the PHC group at most 12-hour intervals after randomization (Asterisk indicates $P \leq .05$).

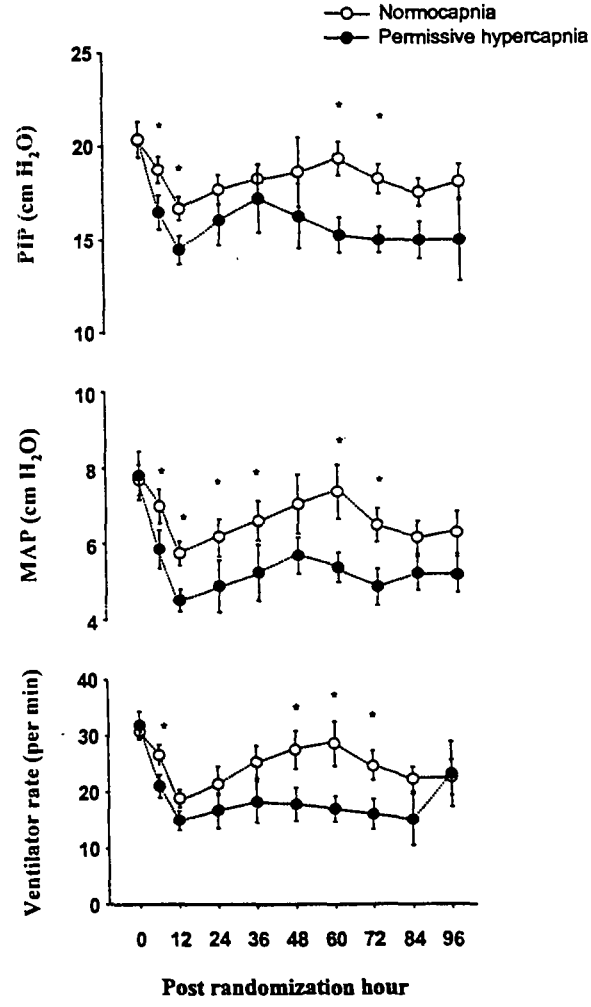

Fig 4. Peak inspiratory pressure (PIP), mean airway pressure (MAP), and ventilator rates in both groups during the first 96 hours after randomization. PIP, MAP, and ventilator rates were lower or comparable in the PHC group (Asterisk indicates $P \leq .05$).

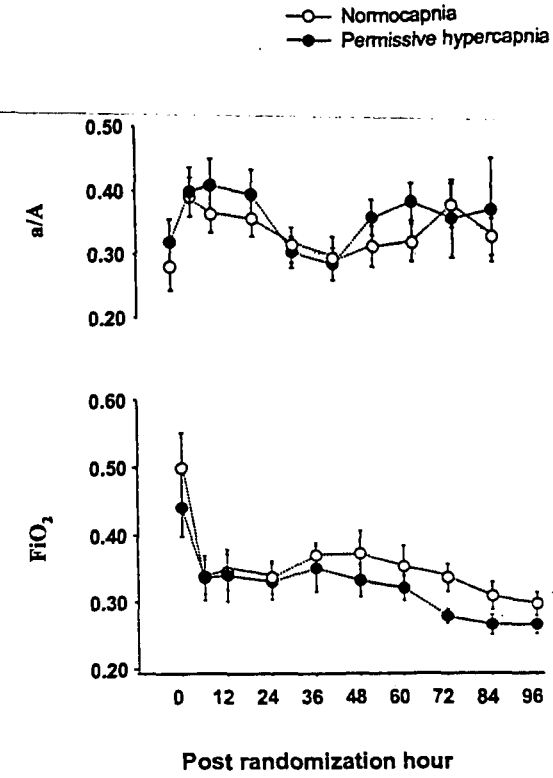

Fig 5. Arterial to alveolar oxygen ratio (a/A ratio) and fraction of inspired oxygen concentration (F_{IO_2}) in both groups during the first 96 hours after randomization. Oxygenation was comparable in the two groups.

show an association between intraventricular hemorrhage and severe ($Paco_2$: ≥60 mm Hg) but not mild hypercapnia.[24,25] $Paco_2$ levels >60 mm Hg also have been associated with the development of retinopathy of prematurity in a mouse model.[26] On the other hand, recent clinical studies suggest that hypocapnia increases the risk for periventricular leukomalacia and cerebral palsy.[27-29] Indeed, it is possible that mild hypercapnia may be protective to the immature brain.[30] Based on this information and on the traditional thought that normal $Paco_2$ levels in ventilated infants are ~40 mm Hg, the target $Paco_2$ ranges selected for this pilot trial were considered safe for both groups. However, tolerance of even higher $Paco_2$ values and/or lower pH values in the PHC group may be acceptable and may have resulted in a larger effect size. Even when the treating physicians followed the protocol, the magnitude of the ventilator changes were sometimes insufficient and may have accounted for the lower than expected levels of $Paco_2$ in the PHC group. Increased spontaneous minute ventilation also may have limited the development of hypercapnia.

The lack of tidal volume measurements in this study may be criticized, because it has been recommended that PHC should be achieved with a reduction in tidal volume. Because tidal volume was not measured in all patients, we cannot relate our results to the tidal volumes used. Experimental and clinical data indicate that ventilator-induced lung injury contributes markedly to lung damage in immature lungs and that the deleterious effect of assisted ventilation is more related to the volumes than to the pressures administered.[31] Thus, the term volutrauma is preferred by some over the commonly used term barotrauma.[32] Tidal volume may be a sensitive indicator of the relative risk of ventilator-induced lung injury.

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TABLE 1. Demographic Data and Prerandomization Ventilator Settings and Blood Gas Values

	Hypercapnia Group (n = 24)	NC Group (n = 25)	P Value
Birth weight (g)	852 ± 156	856 ± 173	.92
Gestational age (wk)	26 ± 1	26 ± 2	.43
Entry age (h)	8.5 (5.5–14)	9 (5–12)	.81
Black race (%)	62	56	.86
Female (%)	54	56	.89
Twin gestation (%)	21	16	1.0
Antenatal steroids (%)	71	52	.29
Full course steroids (%)	29	36	.83
Cesarean section (%)	62	56	.86
Chorioamnionitis (%)	12	12	1.0
Apgar 1 (median)	3	3	.90
Apgar 5 (median)	7	6	.56
Prerandomization settings			
Peak inspiratory pressure (cm H_2O)	20 (18–23)	20 (17–23)	.98
Mean airway pressure (cm H_2O)	7 (6–9)	8 (6–9)	.59
Rate/minute	30 (22–42)	30 (26–35)	.87
FIO_2	0.35 (0.27–0.48)	0.50 (0.25–0.66)	.44
Prerandomization gases			
pH	7.38 ± 0.08	7.37 ± 0.07	.55
$PaCO_2$ (mm Hg)	37 ± 10	36 ± 8	.86
PaO_2 (mm Hg)	57.5 (50–80)	53 (43–67)	.23
Oxygenation index	4.0 (2.9–6.3)	5.3 (2.7–10.9)	.50
Arterial to alveolar oxygen ratio	0.31 ± 0.18	0.29 ± 0.19	.69

Data given as median (25th–75th percentile) for nonparametric tests and as mean ± SD for parametric tests.

TABLE 2. Respiratory Outcomes

	Hypercapnia Group	NC Group	P Value	RR (95% CI)
Assisted ventilation (d)*	2.5 (1.5–11.5)	9.5 (2.0–22.5)	.17	
Supplemental oxygen (d)*	15 (4–53)	32 (17–50)	.34	
BPD (%)	43 (9/21)	64 (14/22)	.29	0.67 (0.35, 1.29)
Oxygen at 36 weeks (%)	10 (2/21)	9 (2/22)	1.0	1.05 (0.11, 10.10)
Air leaks (%)	8 (2/24)	16 (4/25)	.67	0.52 (0.07, 3.08)
Reintubation rate				
Within 24 h (%)	17 (4/24)	28 (7/25)	.54	0.60 (0.16, 2.0)
Any time (%)	67 (16/24)	48 (12/25)	.30	1.39 (0.80, 2.36)
Reintubations for apnea (%)	21 (5/24)	12 (3/25)	.46	1.74 (0.40, 8.74)
Postnatal steroids (%)	12 (3/24)	24 (6/25)	.46	0.52 (0.11, 2.11)
One course	4 (1/24)	12 (3/25)	.61	0.35 (0.01, 3.55)
More than one course	8 (2/24)	12 (3/25)	1.0	0.69 (0.08, 4.86)
Surfactant (doses)*	2 (1–3)	3 (2–3)	.21	
Extubated to NCPAP (%)	25 (6/24)	40 (10/25)	.27	0.63 (0.23, 1.59)

CPAP indicates continuous positive airway pressure. BPD and oxygen at 36 weeks are reported for survivors only.
Relative risk (RR) was calculated for the dichotomous outcome measures.
* Data given as median (25th–75th percentile).

tion of assisted ventilation, we defined and followed strict extubation and reintubation criteria and used precise indications for those therapies that have been reported to influence extubation success, such as aminophylline[17] and dexamethasone.[21]

PHC was compared with NC during the first 96 hours based on two reasons. First, the available evidence relates BPD/CLD to aggressive ventilation in the early (<96 hours) course of respiratory disease.[4,5] Second, after the first few days of treatment, it is common practice in our unit to allow $PaCO_2$ levels to rise, so a consensus was reached among the neonatologists to allow $PaCO_2$ increases in the NC group also after the first 96 hours. The range of safe levels of $PaCO_2$ in neonates is unknown. The benefits of PHC may be counterbalanced by the potential adverse consequences of mild hypercapnic acidosis. Severe hypercapnic acidosis increases cerebral blood flow, which may lead to cerebral edema, increased intracranial pressure, and intraventricular hemorrhage.[22,23] However, data collected retrospectively

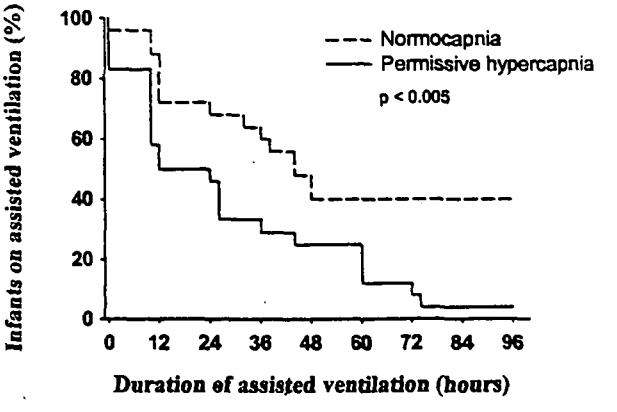

Fig 2. Kaplan-Meier analysis comparing the duration of assisted ventilation during the first 96 hours after randomization in the two groups. The duration of assisted ventilation is expressed as the cumulative number of hours. The number of patients receiving assisted ventilation during the 96 hours after randomization was lower in the PHC group ($P < .005$ by log rank test).

TABLE 3. Nonrespiratory Outcomes

	Hypercapnia Group	NC Group	*P* Value	RR (95% CI)
Mortality (%)	12 (3/24)	12 (3/25)	1.0	1.04 (0.18, 6.16)
IVH (%)	46 (11/24)	56 (14/25)	.67	0.82 (0.43, 1.52)
IVH 3–4 (%)	29 (7/24)	20 (5/25)	.67	1.46 (0.47, 4.82)
Progression of IVH (%)	28 (6/21)	32 (8/25)	.94	0.89 (0.31, 2.43)
PVL (%)	8 (2/24)	8 (2/25)	1.0	1.04 (0.11, 10.10)
ROP ≥stage II (%)	4 (1/24)	4 (1/25)	1.0	1.04 (0.03, 37.75)
PDA (%)	0 (0/24)	12 (3/25)	.23	0
NEC ≥II A (%)	21 (5/24)	8 (2/25)	.24	2.60 (0.49, 18.87)
Pneumonia/proven sepsis (%)	29 (7/24)	52 (13/25)	.18	0.56 (0.24, 1.23)
Length of stay (d)	74 ± 22	76 ± 21	.78	

IVH indicates intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; and CI, confidence interval.
Progression of IVH data is reported for the patients that had a cranial ultrasound before randomization.
Relative risk (RR) was calculated for the dichotomous outcome measures.

However, tidal volumes may vary markedly during pressure-limited ventilation. Furthermore, the uniform practice of $Paco_2$ analysis and the infrequent routine use of tidal volume measurements in neonates make our approach more generalizable.

PHC has not been evaluated previously in a controlled study in neonates. A low mortality rate with the use of PHC has been reported in children[33] and adults[8–11] with acute respiratory distress syndrome and in neonates with persistent pulmonary hypertension.[34] A report of 151 patients weighing ≤1500 g, managed with a protocol emphasizing minimization of ventilatory support, suggested that the use of low ventilator settings may reduce the incidence of pneumothorax and lung injury in neonates who receive assisted ventilation.[35] Two large retrospective studies, designed to determine risk factors for BPD/CLD, concur on the importance of ventilatory strategies.[4,5] Using multiple logistic regression analysis, these two studies independently concluded that ventilatory strategies that lead to hypocapnia during the early neonatal course result in an increased risk of BPD/CLD (relative risk: 1.45; 95% confidence interval: 1.04–2.01; odds ratio: 3.3; 95% confidence interval: 1.3–8.3). Kraybill et al[4] performed a multicenter analysis in 235 infants with birth weights between 751 and 1000 g admitted to 10 neonatal units. In this study, only low levels of $Paco_2$ on days 2 and 4 of life and male gender were independent predictors of BPD (defined as receiving oxygen at 30 days of life). With a similar design, Garland et al[5] analyzed data on 188 patients weighing <1700 g at birth. They observed that low levels of $Paco_2$ on the first day of life remained associated with CLD (defined as receiving oxygen at 36 weeks' gestational age) even when several typical measures of respiratory illness severity were put into the model. Peak levels of $Paco_2$ >50 mm Hg in the first 4 days of life and $Paco_2$ ≥41 mm Hg before the administration of surfactant were reported to be associated with a lower incidence of BPD/CLD in these two studies, respectively. The lack of a statistically significant reduction in the incidence of BPD in the current pilot study may be attributable to a type II error caused by the relatively small sample size.

Hypercapnia has physiologic effects on gas exchange that should provide important benefits. The ventilatory requirements in patients with respiratory failure are determined by the targeted $Paco_2$.[36,37] If $Paco_2$ is permitted to increase, alveolar CO_2 will increase. The increase in alveolar CO_2 that occurs during PHC increases CO_2 elimination for the same minute ventilation. Thus, as CO_2 equilibrates at a higher level in the body, alveolar ventilation requirements decrease because the higher alveolar CO_2 makes elimination more effective. Furthermore, for a given Pao_2 the shift to the right of the oxygen dissociation curve during hypercapnia (Bohr effect) permits more unloading of oxygen to the tissues. Cardiac output may improve as a result of the decreased mean airway pressure that can be used during PHC. The possible negative effects of PHC, thought to be of less clinical importance, include, among others, a small reduction in Pao_2 as a result of the increased alveolar CO_2, a reduction in the transported oxygen in the arterial blood as a result of the right shift of the O_2 dissociation curve, and the potential increases in work of breathing, pulmonary vascular resistance, and cerebral blood flow.[6,7,9,10,36,37]

PHC has been recommended as the preferred ventilatory strategy for the management of acute respiratory distress syndrome,[37] although the data to support its use are limited. The data on potential benefits of PHC in neonates come from retrospective studies. Despite the extraordinarily common use of assisted ventilation in neonates, few prospective, randomized trials have been conducted to determine strategies that limit the severity or prevent the development of BPD/CLD in neonates requiring assisted ventilation. The results of this pilot study provide additional evidence that PHC is likely to be a safe alternative to the traditional normocapnic approach and may reduce lung injury and the duration of assisted ventilation. Moreover, PHC may be combined with other promising techniques such as high frequency ventilation[17] and tracheal gas insufflation.[38] However, caution must be exercised before widespread use of PHC as a mode of assisted ventilation in preterm infants. The small sample size, the relatively low incidence of some of the outcome measures and adverse events, and the wide confidence intervals of the treatment effects preclude firm conclusions about potential benefits or adverse effects of PHC. Additional clinical trials to evaluate the effect of PHC in neonates are warranted.

ACKNOWLEDGMENTS

This work was supported in part by Grant M01-RR00032 from the National Institutes of Health.

We thank the respiratory therapists, nurses, residents, fellows, and attending physicians whose collaboration made this trial possible. We also thank Cassandra Hudson and Maria G. Peroni, who helped us in the preparation of the manuscript.

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June 2, 2000

Waldemar A. Carlo, M.D.
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Birmingham, Alabama 35243

Dear Wally,

This is to confirm my interest in participating in projects undertaken by the multicenter network of neonatal intensive care units.

I would be willing to work with you on designated projects. I would, of course, need more information about each project, risk/benefit considerations, etc.

As you know, my research interests have always been clinically based. I am excited about the possibility of being a part of well planned, well designed nationl multicenter trials to investigate issues of importance in the clinical care of newborns.

Sincerely,

Martha Strange, M.D.

MJS/jjm

NEWBORN CARE P.C.

TERRY M. BIERD, M.D.
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June 15, 2000

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Birmingham, AL 35233

Dear Wally,

We are glad to confirm that we continue to be interested in enrolling patients in studies performed by the NICHD Neonatal Research Network. If invited to participate, we would like to get detailed information to get IRB approval at St. Vincent's Hospital.

We look forward to working with you on this exciting venture.

Sincerely,

Terry M. Bierd, M.D.
NewBorn Care, P.C.
St. Vincent's NICU

R. Dean Bruce, M.D.
NewBorn Care, P.C.
Medical Director
St. Vincent's NICU

2660 10th Avenue South
Suite 636
Birmingham, AL 35205
Phone 205·930·2220
FAX 205·930·2223

Jefferson Health System
COOPER GREEN HOSPITAL
JEFFERSON OUTPATIENT CARE

June 1, 2000

Wally Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
525 New Hillman Building
619 South 20th Street
Birmingham AL 35233

Dear Wally:

It was a pleasure visiting with you and discussing the competitive renewal application for the grant, "Cooperative Multicenter Neonatal Research Netwrok." I have reviewed your performance, and the material from the National Institute of Child Health and Human Development and remain enthusiastic regarding possible participation in Network studies if you need to expand your enrollment to include additional hospitals. I am confident that we are uniquely qualified to be a part of such a network. Briefly, Cooper Green Hospital provides perinatal-neonatal services to over 1320 inborn patients annually. The patient population is largely indigent patients of Jefferson County. I have participated with your Division and with the Infectious Disease division in prospective clinical studies for the past several years.

As I mentioned during our conversation, any protocol would have to have formal approval of the appropriate committees (i.e., Research and Human Use) at this hospital and ultimately the Board of Trustees. I would also like to emphasize that the hospital would have to be reimbursed for any additional cost that such studies would generate.

I would be pleased to serve as one of the Level III units in this project, and welcome the opportunity to assist in investigation of safe and efficient management strategies for NICU patients.

Please let me know if I can provide further information.

Sincerely,

Santosh

Santosh K. Khare, M.D., M.P.H.
Director, NICU and Newborn Service
Cooper Green Hospital
Clinical Professor of Pediatrics - UAB

SKKlmn

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JEFF GERMANY, COMMISSIONER
Health and Human Services
MAX MICHAEL, M.D.
Chief Executive Officer and Medical Director

UAB SCHOOL OF MEDICINE
Neonatology Services

UAB Hospital, Children's Hospital,
Baptist Health System, Eastern Health
System, Carraway Health System

June 28, 2000

Waldemar A Carlo, M.D.
Professor of Pediatrics
Director, Division of Neonatology
Medical Director of Nurseries
University of Alabama at Birmingham
525 New Hillman Building
619 South 20th Street
Birmingham, AL 35233

Dear Wally:

We have been very impressed with the NICHD Multicenter Neonatal Research Network trials and would like to offer our four community Neonatal Intensive Care Units for possible studies. We have enjoyed participation in the care of patients enrolled in the trials at UAB and feel that conducting selected studies in the community NICUs will be possible. As you know two of our community NICUs enrolled patients in non-Network studies as part of our collaboration with UAB.

Thanks for the opportunity to collaborate in this effort.

Sincerely,

James Haywood, M.D.
Medical Director, Baptist Health Systems NICUs
Carraway Methodist Medical Center NICU

Carl H. Coghill, III, M.D.
Medical Director, The Children's Hospital of Alabama NICU

Virginia Karle, M.D.
Medical Director, Bessemer Carraway Medical Center NICU
Medical Center East NICU

The University of Alabama at Birmingham
Section of Clinical Neonatology
P.O. Box 131424
Birmingham, Alabama 35213
Voice (205) 592-0551
FAX (205) 592-0553

Carl H. Coghill, III, M.D.
James L. Haywood, M.D.
Virginia A. Karle, M.D.

DCH Regional Medical Center

809 University Boulevard East
Tuscaloosa, Alabama 35401
205.759.7111

June 8, 2000

Wally Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
525 New Hillman Building
619 South 20th Street
Birmingham, AL 35233

Dear Wally:

As we discussed on the phone, we will be able to enroll infants in the Multicenter Neonatal Research Network if an expanded network is needed.

I have always been enthusiastic about doing clinical research. We have performed and published clinical trials on massage (L Harrison et al.).

Please let me know how we can help.

Sincerely,

Guillermo Godoy, M.D.
Chairman, Department of Pediatrics, DCH Regional Medical Center
Director, Department of Neonatology, DCH Health System

GG/eg

DCH Health System

Huntsville Neonatology, P.C.

Meyer E. Dworsky, M.D. Thomas H. Davison, M.D.

June 8, 2000

Wally Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
525 New Hillman Building
619 South 20th Street
Birmingham, Alabama 35233

Dear Wally:

I am glad to inform you that we could enroll patients in the NICHD Neonatology Network if necessary. We admit over 500 infants to our NICU per year. This large number of infants could be useful for selected studies requiring an expanded Network.

Please let me know if any studies come up in which we could help.

Sincerely,

Meyer E. Dworsky, M.D., Medical Director
Huntsville Hospital Level III NICU

MED/mmh

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OFFICE ADDRESS: Suite A-202 • 115 Manning Drive • Huntsville, Alabama 35801
MAILING ADDRESS: Post Office Box 2289 • Huntsville, Alabama 35804
TELEPHONE: (256) 536-9587 FACSIMILE: (256) 536-9588

UNIVERSITY OF SOUTH ALABAMA
HOSPITALS

CHILDREN'S AND WOMEN'S HOSPITAL
COLLEGE OF MEDICINE
DEPARTMENT OF PEDIATRICS
DIVISION OF NEONATAL MEDICINE

TELEPHONE: (334) 415-1055
1700 CENTER STREET
MOBILE, ALABAMA 36604-3391
FAX: (334) 415-1045

Fabien G. Eyal, M.D.
Louis Lenoir Locke
Professor of Pediatrics
Chief and Medical Director
(334) 415-1055
feyal@jaguar1.usouthal.edu

Hollis J. Wiseman, M.D.
Professor Emeritus
(334) 415-1055

Keith J. Peevy, M.D.
Professor
(334) 415-1055

Charles R. Hamm, Jr., M.D.
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Assistant Professor
(334) 415-1055
rwhitehu@jaguar1.usouthal.edu

Michael M. Zayek, M.D.
Assistant Professor
(334) 415-1065

June 6, 2000

Wally Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
525 New Hillman Building
619 South 19th Street
Birmingham, Alabama 35233

Dear Dr. Carlo:

Thank you for inviting us to support your grant application for the NICHD Cooperative Multicenter Neonatal Research Network.

Our Neonatal Intensive Care Nursery serves a very large population (we continually exceed 800 admissions every year). Our 80-bed unit would be available to perform Network studies that require a broad segment of the State population.

We earnestly support your grant application and are excited about the possible participation in the Neonatal Network trials.

Sincerely,

Fabien G. Eyal, M.D.
Professor of Pediatrics
Chief and Louise Lenoir Locke Professor of of Neonatology
Medical Director, Southwest Regional Intensive Care Nurseries

FGE/klm

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ALABAMA NEONATAL MEDICINE, P.C.

Neonatal-Perinatal Medicine

J. Allen Newton, M.D.
Board Certified
Neonatal-Perinatal Medicine

Lynn K. Whittington, M.D.
Board Certified
Neonatal-Perinatal Medicine

J. Allan Cheek, Jr., M.D.
Board Certified
Neonatal-Perinatal Medicine

Lawrence A. Wallin, M.D.
Board Certified
Neonatal-Perinatal Medicine

Cynthia M. Bonner, M.D.
Board Certified
Neonatal-Perinatal Medicine

John B. Woodall, M.D.
Board Certified
Neonatal-Perinatal Medicine

June 1, 2000

Wally Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
525 New Hillman Building
619 South 20th Street
Birmingham, AL 35233

Dear Wally:

It was good to discuss your application for renewal of the NICHD Neonatal Network grant. As with our collaboration in the CryoROP study, we would be glad to participate in patient enrollment. We would be willing to work with you on designated projects. We have six Neonatologist on staff that provide attending coverage for Jackson Hospital, Baptist Medical Center East (BMC-E), and Baptist Medical Center South (BMC-S). We serve as the neonatal referral center for 23 counties in South East and South Central Alabama and our combined NICU admission to BMC-E and BMC-S exceeded 500 in 1999. Our large patient population could help in studies requiring a large patient base. We would welcome the opportunity to assist in investigational studies that may have an impact on improved outcome for our patients and/or serve to broaden our understanding of the pathophysiologic basis of new investigational treatments.

Sincerely,

Allen Newton, M.D.
Medical Director, BMC RNICU

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Baptist Towers - Suite 611 • 2055 East South Blvd. • Montgomery, AL 36116-2462
Business Office: 334-284-0353 or 0354 • Facsimile: 334-284-8417

June 26, 2000

Waldemar A. Carlo, M.D.
UAB Medical Center
Division of Neonatology
525 New Hillman Building
619 South 20th Street
Birmingham, AL 35233

Dear Wally:

As President of the Alabama Society of Neonatology, I want to inform you that we will continue supporting recruitment efforts for selected trails of the NIH Neonatal Research grant, including the hypothermia trial.

The Alabama Society of Neonatology is already participating in the collection and analyses of morbidity and mortality data for infants with birth weights less than 1500 grams. In our regular annual and quarterly meetings we will continue to discuss clinical and academic controversies as well as potential participation in Network studies.

We will be very interested in being part of this Network for these clinical research projects. Please let me know about other protocols in which we could refer patients.

Sincerely,

Guillermo Godoy, M.D.
Co-Director Neonatal Intensive Care
DCH Regional Medical Center
President, Alabama Society of Neonatology

REGIONAL NICU AT UAB
ADMISSIONS – MARCH 2000

	NAME	HOSP #	BW (Kg)	SEX	GA (Weeks)	ADMITTING DIAGNOSIS (Other Than Maturity)	ADM DATE
1	J.S.	1657808	1399	M	30	r/o sepsis	3/01/00
2	A.W.	1646126	638	M	24	RDS, r/o sepsis	3/01/00
3	T.S.	1657792	3416	F	34	Hydrops, RDS, r/o sepsis	3/01/00
4	M.H.	1657424	2157	M	34	Right upper quadrant mass (hemangioendothelioma)	3/02/00
5	V.A.	1658033	3033	M	36	TTN	3/02/00
6	J.R.	1658131	3301	F	40	ABO incompatibility	3/02/00
7	T.L. #1	1658174	2420	M	34	IDM, r/o sepsis	3/03/00
8	T.L. #2	1658175	2123	F	34	IDM, r/o sepsis	3/03/00
9	K.C. #1	1658585	837	F	26	RDS, r/o sepsis	3/03/00
10	K.C. #2	1658589	824	F	26	RDS, r/o sepsis	3/03/00
11	J.R. #1	1658586	2082	M	32	r/o sepsis	3/03/00
12	J.R. #2	1658587	2110	M	32	r/o sepsis	3/03/00
13	I.M.	1658560	761	F	28	RDS, r/o sepsis, anemia	3/03/00
14	J.A. #1	1658567	2288	M	32	RDS, r/o sepsis	3/03/00
15	J.A. #2	1658569	2502	M	32	RDS, r/o sepsis	3/03/00
16	T.R.	1658390	3569	M	39	Myelomeningocele	3/03/00
17	E.D.	1658627	885	F	28	RDS, r/o sepsis	3/04/00
18	P.M.	1628635	2644	M	34	r/o sepsis	3/05/00
19	J.M.	1658631	2579	M	34	RDS, r/o sepsis	3/05000
20	K.M.	1658651	3089	F	39	PPHN, r/o sepsis	3/05/00
21	B.I.	1658642	4380	M	40	PPHN, LGA	3/05/00
22	A.T. #1	1659030	709	F	25	RDS, r/o sepsis	3/06/00
23	A.T. #2	1659031	650	F	25	RDS, r/o sepsis	3/06/00
24	T.R.	1658822	847	F	28	RDS, r/o sepsis	3/06/00
25	A.C.	1658825	1135	F	34	SGA, r/o sepsis	3/06/00
26	S.W.	1659038	4075	F	41	r/o sepsis, LGA, MAS	3/07/00
27	A.Y.	1659036	2376	M	34	r/o sepsis	3/07/00
28	B.I.	1659071	498	M	23	RDS	3/07/00
29	P.S.	1659287	2680	F	37	r/o sepsis	3/07/00
30	T.B.	1659351	1495	F	32	r/o sepsis	3/07/00
31	J.C.	1659358	2951	F	37	Sacrcoccygeal teratoma	3/07/00
32	G.J.	1659434	3750	F	37	Truncus type IV and total anomalous pulmonary venous return	3/08/00
33	L.S.	1659729	3668	M	41	r/o sepsis	3/09/00
34	J.T.	1660015	1524	F	31	r/o sepsis	3/09/00
35	A.T.	1660000	2735	M	35	TTN, hypoglycemia	3/09/00
36	S.G.	1660107	2255	M	34	r/o sepsis	3/10/00
37	C.A.	1660159	3190	F	34	Pulmonary atresia, r/o sepsis	3/10/00
38	K.A.	1660314	619	M	26	RDS, r/o sepsis	3/11/00
39	B.B.	1660360	2420	M	35	TTN	3/11/00
40	B.W.	1660345	2408	F	37	Tetralogy of Fallot	3/11/00
41	K.P.	1660331	3764	M	39	r/o sepsis	3/11/00
42	A.B.	1660338	2274	M	34	r/o sepsis	3/11/00

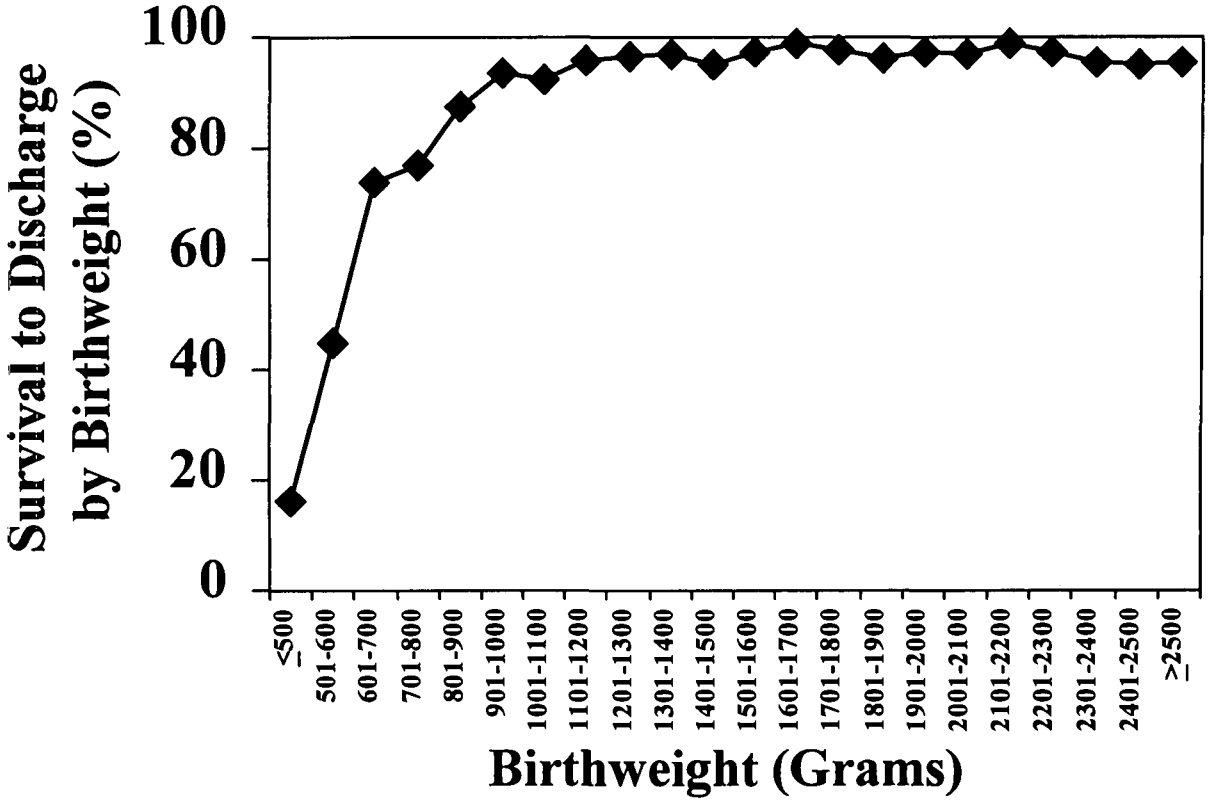
43	H.G.	1660330	1373	F	33	r/o sepsis	3/11/00
44	M.A.	1660354	902	M	27	RDS, r/o sepsis	3/11/00
45	C.S.	1660375	3608	F	40	r/o sepsis	3/12/00
46	D.W.	1660805	3077	M	39	r/o sepsis	3/13/00
47	D.G.	1660850	2098	M	34	r/o sepsis	3/13/00
48	J.S.	1654196	910	M	26	Post hemorrhagic hydrocephalus, status post placement of ventricular shunt	3/13/00
49	T.P. #1	1660851	1873	M	31	r/o sepsis	3/13/00
50	T.P. #2	1660852	2318	M	31	RDS, r/o sepsis	3/13/00
51	M.G.	1660679	755	F	31	RDS, r/o sepsis	3/13/00
52	H.B.	1660988	3051	F	39	Myelomingocele	3/14/00
53	P.M.	1661125	1207	F	29	RDS, r/o sepsis	3/15/00
54	T.M.	1660930	3170	F	41	r/o sepsis	3/15/00
55	C.S.	1661452	3520	M	40	Cleft lip and palate	3/15/00
56	I.E.	1661344	3163	M	40	PPHN, sacral mass, r/o sepsis	3/15/00
57	M.B.	1661462	1892	F	36	r/o sepsis	3/16/00
58	N.H.	1661460	1509	M	31	r/o sepsis, hyperbilirubinemia	3/16/00
59	B.B. #1	1661843	1787	M	32	Anemia, r/o sepsis, r/o congenital syphilis	3/17/00
60	B.B. #2	1661844	1802	M	32	r/o congenital syphilis, r/o sepsis	3/17/00
61	T.J.	1661838	1908	F	32	r/o sepsis	3/17/00
62	T.R.	1662082	3289	F	38	Interrupted aortic arch	3/17/00
63	H.B.	1662053	630	F	23	RDS, r/o sepsis, hypoglycemia	3/17/00
64	T.C.	1662103	1547	F	29	r/o sepsis	3/18/00
65	S.B.	1662096	4135	F	39	LGA, r/o sepsis	3/18/00
66	B.M.	1662128	900	M	28	RDS, r/o sepsis	3/18/00
67	C.S. #1	1662149	1392	F	32	ABO incompatibility, r/o sepsis	3/19/00
68	C.S. #2	1662150	1520	M	32	ABO incompatibility, r/o sepsis	3/19/00
69	K.C.	1662136	387	F	23	RDS, r/o sepsis	3/19/00
70	A.S.	1662140	2180	M	36	Apnea, r/o sepsis	3/19/00
71	A.H.	1662119	3655	M	40	Pneumothorax, r/o sepsis	3/19/00
72	E.E.	1662157	2737	M	34	Meningocele	3/19/00
73	M.F.	1662307	1060	F	32	Ventricular septal defect, r/o sepsis	3/20/00
74	C.L.	1662159	3890	F	38	Arnold-Chiari malformation	3/20/00
75	D.A.	1662301	4405	F	42	LGA, r/o PPHN, r/o sepsis	3/20/00
76	L.S. #1	1662447	688	F	26	RDS, r/o sepsis	3/20/00
77	L.S. #2	1662451	600	F	26	RDS, r/o sepsis	3/20/00
78	L.L.	1662661	1400	M	34	Coarctation of the aorta, RDS, r/o sepsis, hypospadia	3/20/00
79	V.L.	1662810	472	M	23	RDS, r/o sepsis	3/21/00
80	S.B.	1662815	3150	F	40	PPHN, anemia, r/o sepsis	3/21/00
81	L.M.	1662820	1403	F	31	RDS, r/o sepsis	3/21/00
82	M.J.	1663096	2549	M	37	r/o sepsis	3/22/00
83	V.T.	1663080	1238	F	29	RDS, r/o sepsis	3/22/00
84	C.A.	1662929	690	M	25	RDS, r/o sepsis	3/22/00
85	A.B.	1663107	2304	F	35	r/o sepsis	3/23/00
86	B.C.	1662162	3433	M	36	Supraventricular tachycardia	3/19/00
87	T.G.	1663426	2462	M	34	r/o sepsis	3/24/00
88	J.M.	1658631	2579	M	34	RDS, r/o sepsis	3/15/00

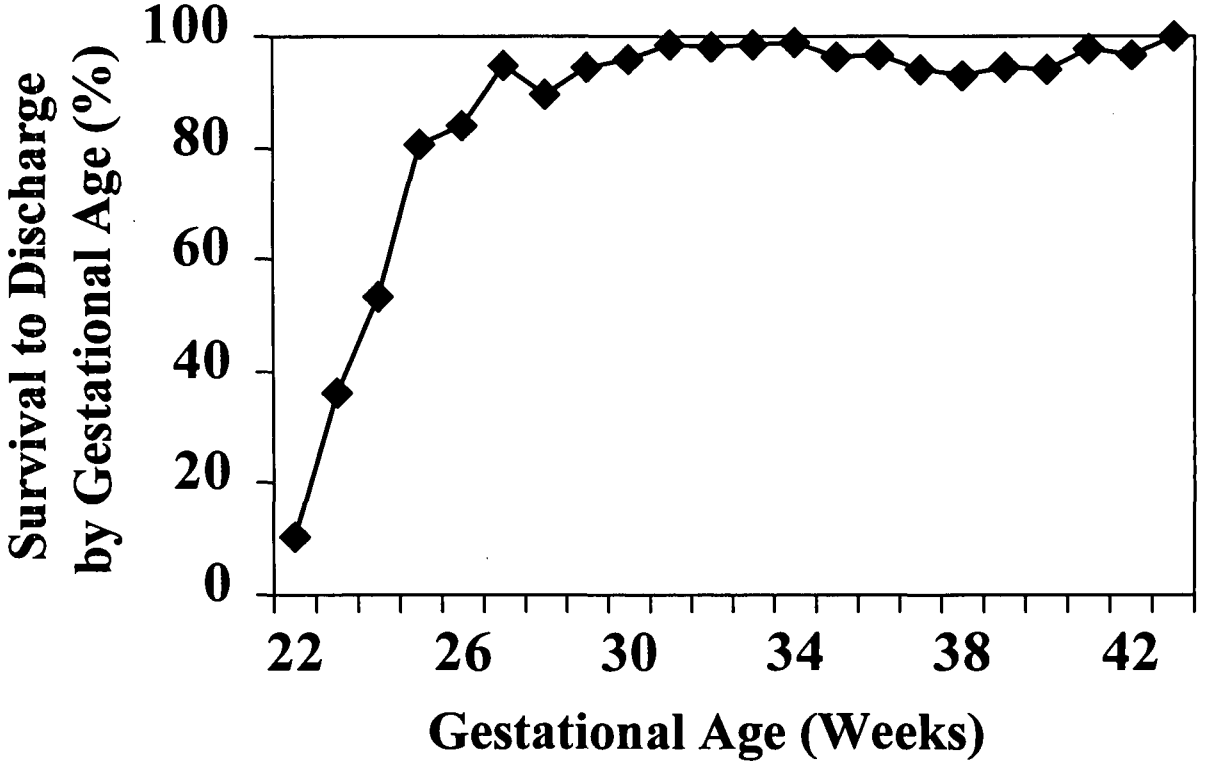
89	N.K.	1663597	1021	F	27	r/o sepsis	3/24/00
90	G.S.	1663503	3733	F	40	Fetal distress	3/24/00
91	J.M.	1663564	1808	M	31	Congenital herpes	3/24/00
92	K.T.	1663636	694	M	24	RDS, r/o sepsis	3/25/00
93	S.V.	1663685	1951	F	31	r/o sepsis	3/26/00
94	A.F.	1663688	1092	M	29	RDS, r/o sepsis	3/27/00
95	Y.N.	1663942	1716	F	32	r/o sepsis	3/27/00
96	L.W.	1663935	3516	M	38	r/o sepsis	3/27/00
97	L.R.	1664222	2180	F	36	Congenital syphilis, maternal hepatitis B	3/28/00
98	K.F.	1664519	2860	M	39	MAS, r/o sepsis, bilateral club feet	3/29/00
99	L.H.	1664550	3673	F	34	Omphalocele, Beckwith Wiedemann syndrome, RDS, r/o sepsis	3/29/00
100	S.S.	1664749	3777	M	40	Hypoplastic left ventricle with aortic atresia	3/30/00
101	R.M.	1664780	2316	F	34	r/o sepsis	3/30/00
102	S.S.	1664926	898	F	29	RDS, r/o sepsis, hypoglycemia	3/31/00

Abbreviations Used

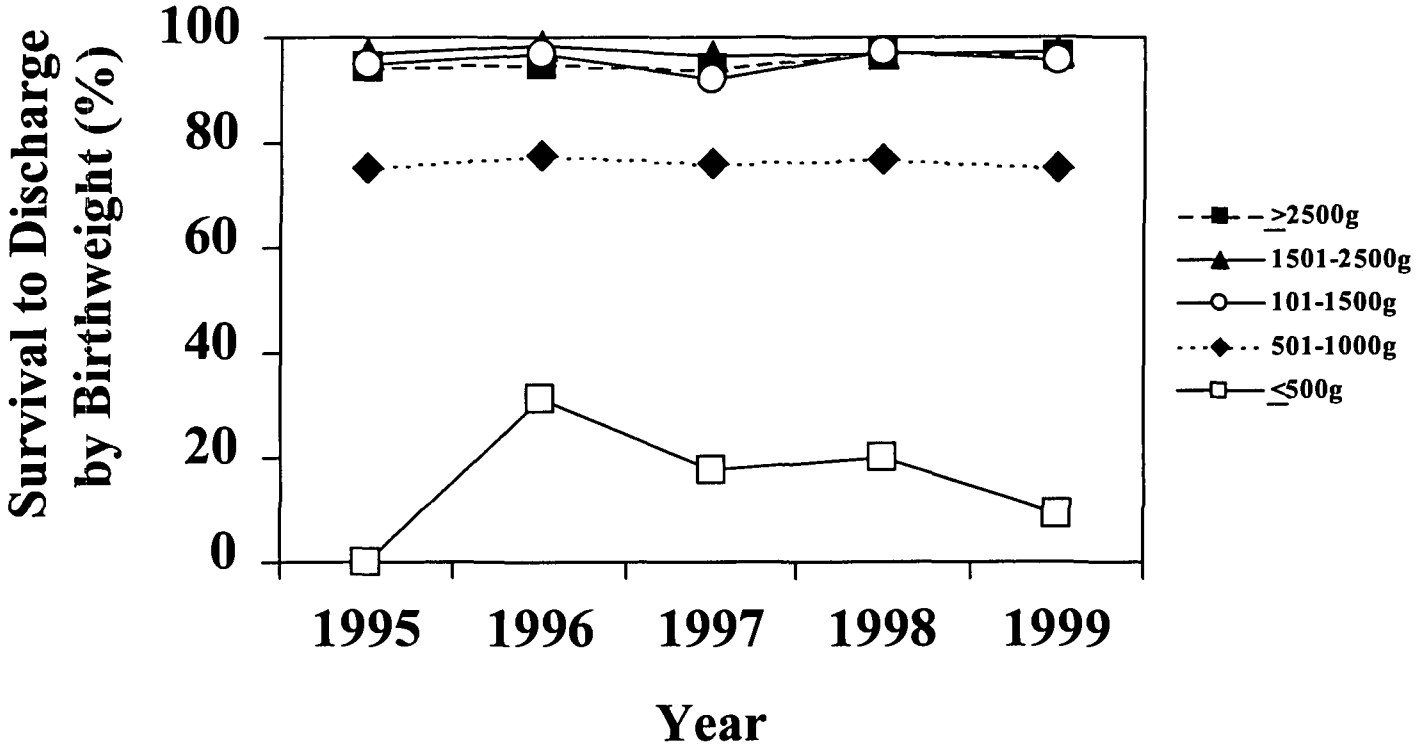
IDM – infant of a diabetic mother
LGA – large for gestational age
MAS – meconium aspiration syndrome
PPHN – persistent pulmonary hypertension of the newborn
RDS – respiratory distress syndrome
SGA – small for gestational age
TTN – transient tachypnea of the newborn

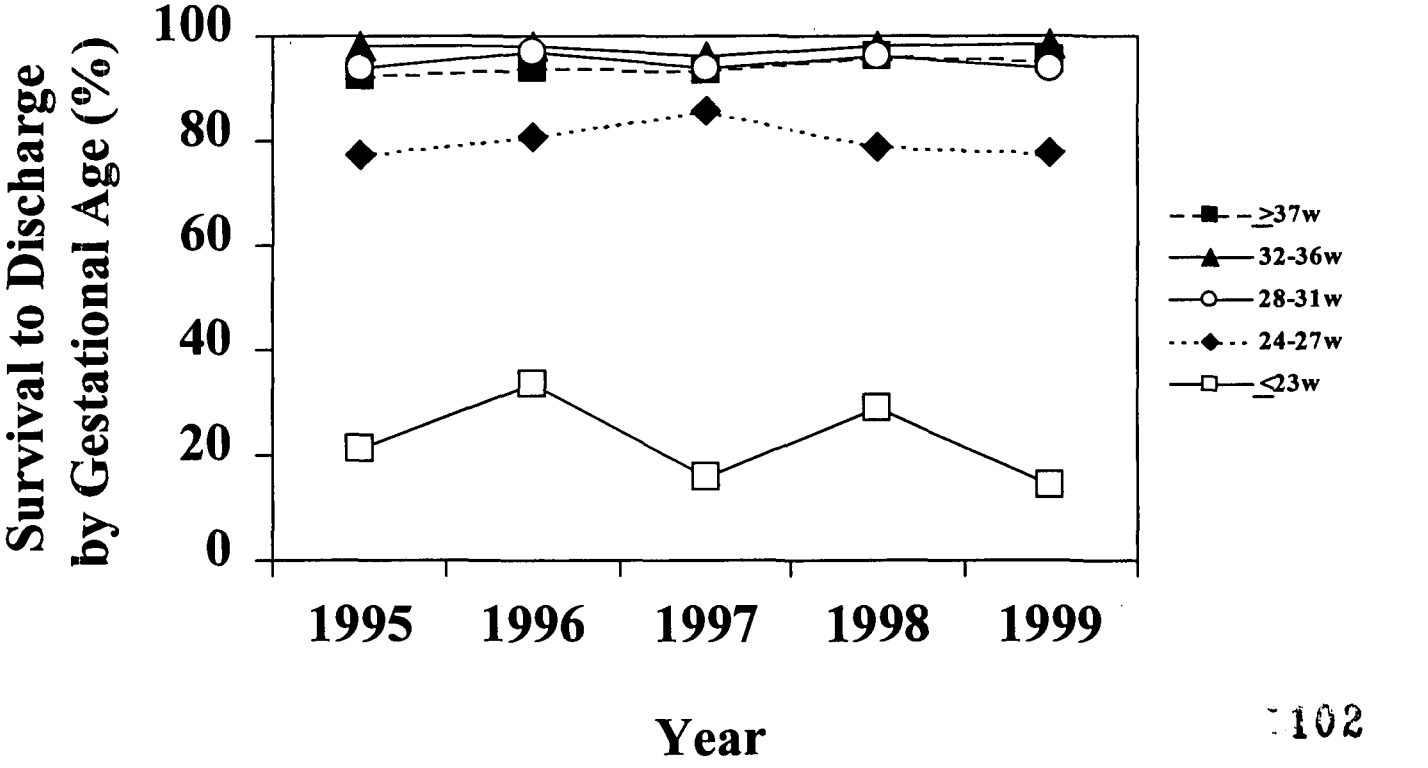
Survival to Discharge of Neonates Requiring Admission to the Regional NICU at UAB for the Years of 1995 to 1999





Survival to Discharge of Neonates Requiring Admission to the Regional NICU at UAB for the Years of 1995-1999





UAB UNIVERSITY HOSPITAL

OB/GYN DEPARTMENT - LABOR and DELIVERY AREA
PHYSICIAN'S ADMISSION HISTORY and PHYSICAL FORM

Keyplate

DATE ___/___/___ TIME: ___ : ___

CIRCLE EACH APPROPRIATE ANSWER

AGE: _____ PARA: ___ ___ ___ ___ RACE: B W O HISTORY PROM: NO YES CONTRACTIONS: NO YES q ___ min
BLEEDING: NO YES DATE: ___/___/___ TIME: ___ : ___ ONSET DATE: ___/___/___ TIME: ___ : ___
CHIEF COMPLAINT/HISTORY:

PRENATAL SOURCE:
01 HEALTH DEPT
02 OBCC
03 MFM
04 PRIMARY OB/GYN ASSOC.
05 NO PRENATAL CARE
06 PHYSICIAN REFERRAL
NAME _____
CITY _____

GESTATION AGE CRITERIA **EDD**
LMP ___/___/___ ___/___/___
1ST ULTRASOUND _____ WKS ON ___/___/___ ___/___/___
BEST ESTIMATE ___/___/___
EGA ON ADMISSION _____ WKS _____ DAYS

ANTENATAL: (Circle Result)
Rh NEG POS
IF NEG, LAST Ab TITER ON ___/___/___
ANTENATAL RHOGAM GIVEN ___/___/___
RUBELLA IMM NONIM
PAP NL AB
VDRL NEG POS
GC(S) NEG POS
LAST PCV _____ ON ___/___/___
DESIRES BTL NO YES
PAST SURGERY _____
PAST MEDICAL _____
ALLERGY _____

EXAM:
ADMIT WEIGHT _____ kg TEMP _____ °
B/P _____/_____ PULSE _____ RESP _____

	NL	COMMENTS
NECK	☐	
BREAST	☐	
CHEST	☐	
HEART	☐	
EXTREM	☐	
NEURO	☐	
ABDOMEN	☐	

FH _____ cm FHR _____ BPM
EFW _____ gm PRES. V B O

	NO	YES
STERILE SPEC.		
GROSS POOLING	0	1
NITRAZINE (+)	0	1
FERNING	0	1
DIL _____ CM		
EFF _____ %		
STN _____		
POS: ANT MID POS		
CONSIS: SOFT MOD FIRM		
Cx CULTURED		
GPB STREP	0	1
HERPES	0	1
CHLAMYDIA	0	1
N. GONORRHEA	0	1

0152

MAJOR ANTEPARTUM PROBLEMS:
00 NONE
01 CHRONIC HYPERTENSION
02 DIABETES CLASS (circle one)
A1 A2 B C D F R GB
03 SUBSTANCE ABUSE
04 FETAL DEMISE (known AP)
05 SEXUALLY TRANSMITTED DISEASE
01 HIV (+) 02 HERPES
03 HEP B 04 SYPHILIS
05 OTHER _____

PROBLEMS:
06 KNOW FETAL ANOMALY
07 MULTIPLE PREGNANCY 1 2 3 4
08 TREATED PRETERM LABOR
09 SUSPECTED FETAL GROWTH RETARDATION
10 AMNIOTIC FLUID DISTURBANCE
01 OLIGOHYDRAMNIOS
02 POLYHYDRAMNIOS
11 PRIOR CESAREAN 01 LT 02 V 03 UNK
12 OTHER _____

MEDS ON ADMISSION
00 NONE
01 INSULIN
02 ANTI-HYPERTENSIVES
03 ORAL TOCOLYTIC
04 CORTICOSTEROD
05 HEPARIN

LABS ON ADMISSION
PCV _____
URINE PROTEIN _____

ANTEPARTUM TESTING DATA
PULMONARY MATURITY TEST
LAST L/S _____ ___/___/___
LAST PG _____ ___/___/___

FETAL SURVEILLANCE (LAST TEST)
CST 0 NEG 1 POS ___/___/___
NST 0 R 1 NR ___/___/___

ASSESSMENT **PLAN**

RESIDENT _____, M.D. ATTENDING _____, M.D.

IF DISCHARGED UNDELIVERED: DISCHARGED DATE ___/___/___

TREATMENT/MEDS	IN HOSP	DISCHARGED
_____	0	1
_____	0	1
_____	0	1
IF PTL	0	1
01 B-MIMETIC	0	1
02 MgSO4	0	1
03 INDOMETHACIN	0	1

DIAGNOSIS _____

CLINIC _____ APPT. DATE ___/___/___

RESIDENT _____, M.D. ATTENDING _____, M.D.

UAB UNIVERSITY HOSPITAL

INTRAPARTUM DATA

Keyplate

DATE ___/___/___ TIME: ___ : ___

CIRCLE EACH APPROPRIATE ANSWER

FETUS # _____ OF _____ INFANT MEDICAL RECORD # _____

LABOR
0 NONE
1 SPONT
2 SPONT W/OXYTOCIN AUGMENT.
3 INDUCED (OXYTOCIN)
4 ABORTION
01 PG
02 SALINE
03 CONCENTRATED OXYTOCIN

INTRAPARTUM PROCEDURES
0 NONE
1 MATERNAL INTRAVASCULAR MONITORING
2 DILAPAN
3 AMNIO INFUSION
4 SCALPH pH
5 OTHER _____

INTRAPARTUM DRUGS/ANESTHESIA/TREATMENT
0 NONE
1 FOR PIH/PREECLAMPSIA
01 MgSO4
02 APRESOLINE
2 CORTICOSTEROIDS (PUL MATUR.)
3 ANTIBIOTICS
4 TRANSFUSION BLOOD
5 EPIDURAL
FOR TOCOLYSIS/PLAC. PREV.
6 B-MIMETICS
01 IV
02 SQ
03 ORAL
7 MgSO4
8 INDOMETHACIN

INTRAPARTUM COMPLICATIONS
0 NONE
1 HYPERTENSIVE DISEASE
01 PIH
02 PREECLAMPSIA
03 ECLAMPSIA
2 ABRUPTIO PLACENTA
3 PLACENTA PREVIA
4 AMNIONITIS
5 MECONIUM
6 PULMONARY EDEMA
7 SHOULDER DYSTOCIA
8 FETAL DISTRESS MANDATING OPERATIVE DELIVERY
9 ANESTHESIA COMPLICATIONS
01 HYPOTENSION
02 ASPIRATION
10 OTHER _____

MEMBRANES RUPTURED DATE: ___/___/___
1 ARTIFICIAL
2 SPONTANEOUS TIME: ___ : ___ (24 HR CLOCK)

DELIVERY DATE: ___/___/___ **TIME:** ___ : ___ (24 HR CLOCK)

TYPE OF DELIVERY (INCLUDING FAILED ATTEMPTS)
1 SVD
2 OUTLET FORCEPS
3 OUTLET VACUUM
4 LOW FORCEPS
5 LOW VACUUM
6 MID FORCEPS
7 MID VACUUM
8 FORCEP ROTATION (>45°)
9 ASSISTED BREECH EXTRACTION
10 VERSION EXTRACTION
11 CESAREAN
01 LOW TRANSVERSE
02 LOW VERTICAL
03 CLASSICAL
04 C/HYST
05 BTL WITH C/S
12 UTERUS CLOSED IN:
01 ONE LAYER
02 TWO LAYERS
03 THREE LAYERS
13 EXTRA HEMOSTATIC SUTURES NEEDED
14 UTERINE ARTERY LIGATION _____

CESAREAN DELIVERY INDICATED FOR
1 FETAL DISTRESS
2 DYSTOCIA/CPD
3 FAILED INDUCTION
4 REPEAT C/S:
VBAC TRIAL 0 NO 1 YES
5 BREECH/TRANSVERSE LIE
6 PLACENTA PREVIA
7 ABRUPTION
8 SUSPECTED MACROSOMIA
9 MATERNAL INDICATION _____
10 OTHER _____

IF PRETERM DELIVERY
0 NOT APPLICABLE
1 INDICATED (NOT PROM)
2 PROM
01 INDUCED OR C/S
02 SPONTANEOUS LABOR
3 SPONTANEOUS PTL
IF INDICATED, PRIMARY INDICATION: _____

ANESTHESIA FOR DELIVERY
0 NONE
1 LOCAL
2 EPIDURAL
3 GENERAL
4 PUDENDAL
5 SPINAL

NEWBORN
1 APGARS - 1 MIN _____
5 MIN _____
2 BIRTHWEIGHT _____ GMS
3 MALE 4 FEMALE
5 ANOMALIES: 0 NO 1 YES
IF YES, SPECIFY: _____

ARTERIAL CORD BLOOD CHEMISTRIES
pH _____
pCO2 _____
PO2 _____
HCO3 _____

VENOUS CORD BLOOD CHEMISTRIES
pH _____
pCO2 _____
pO2 _____
HCO3 _____

EPISIOTOMY/EXTENSION
0 NONE
1 1°/2°
2 3°
3 MEDIAN 4°
4 MEDIOLATERAL

GENITAL LACERATIONS
0 NONE
1 1°/2°
2 3°
3 4° LACERATION
4 VAGINAL SIDEWALL
5 CERVIX

INFANT DISPOSITION
1 WELLBABY
2 NICU
3 ANTENATAL FETAL DEMISE
4 INTRAPARTUM FETAL DEMISE
5 HOSPICE CARE IN LABOR SUITE
6 IMMEDIATE NEONATAL DEMISE

PLACENTAL/UMBILICAL CORD
1 PLACENTAL WT _____ GMS
2 SPONTANEOUS DELIVERY
3 MANUAL EXTRACTION
4 RETAINED
5 TWO VESSELS
6 NUCHAL X _____
7 OTHER _____

ESTIMATED BLOOD LOSS: _____ **CC**

COMMENTS:

ATTENDING FACULTY _____ / _____ MD
(DICTATION #) (NAME)

RESIDENT _____ / _____ MD
(DICTATION #) (NAME)

ASST. RESIDENT _____ / _____ MD
(DICTATION #) (NAME)

the University of Alabama at Birmingham
the Medical Center/UNIVERSITY OF ALABAMA HOSPITAL

ADDRESSOGRAPH

POSTPARTUM/DISCHARGE DATA

DATE___/___/___ TIME:___:___

CIRCLE EACH APPROPRIATE ANSWER

DEATH
00 NO
01 MATERNAL DEATH

IMMUNIZATIONS

		NOT INDICATED	RECEIVED	INDICATED
01	RUBELLA	00	01	02
02	RHOGAM	00	01	02

POSTPARTUM HEMORRHAGE
00 NONE
01 EARLY < 2 HOURS
02 LATE > 2 HOURS

ETIOLOGY
01 UTERINE ATONY
02 RETAINED PLACENTA
03 CERVICAL LACERATION
05 VAGINAL LACERATION
06 UTERINE RUPTURE
07 HEMATOMA
08 COAGULATION DISORDER

TREATMENT
00 NONE
01 TRANSFUSION (LOWEST PCV _____)

POSTPARTUM PROCEDURES
00 NONE
01 BTL
02 CURETTAGE
03 SECONDARY WOUND CLOSURE
04 HYSTERECTOMY
05 OTHER_____

DISCHARGED
B/P_____/_____
PCV_____

POSTPARTUM INFECTIONS
00 NONE
01 ENDOMETRITIS
02 PELVIC ABSCESS
03 PYELONEPHRITIS
04 WOUND
05 PNEUMONIA
06 EPISIOTOMY
07 SEPTICEMIA

OTHER POSTPARTUM PROBLEMS
00 NONE
01 PUL EMBOLISM/THROMBOPHLEBITIS
02 POSTPARTUM PIH
03 BOWEL OBSTRUCTION/PROLONGED ILEUS
04 RENAL FAILURE
05 WOUND SEROMA/SEPARATION
06 FASCIAL DEHISCENCE
07 OTHER_____

CONTRACEPTIVE CHOICE
01 DECLINED
02 OCP
03 TUBAL LIGATION
01 DONE POSTPARTUM
02 TO BE SCHEDULED
04 BARRIER
05 WILL DECIDE LATER

MEDICATIONS (CIRCLE)

		POSTPARTUM	DISCHARGE
00	NONE		
01	LACTATION SUPPRESSION	01	02
02	ORAL CONTRACEPTIVES	01	02
03	ANTIHYPERTENSIVES	01	02
04	INSULIN	01	02
05	PENICILLIN	01	02
06	AMPICILLIN	01	02
07	AMINOGLYCOSIDE	01	02
08	CLINDAMYCIN	01	02
09	CEPHALOSPORIN	01	02
10	FLAGYL	01	02
11	CHLORAMPHENICOL	01	02
12	FESO4	01	02

OTHER:

13	_____	01	02
14	_____	01	02
15	_____	01	02
16	_____	01	02
17	_____	01	02

COMMENTS:

FOLLOW/UP NEEDED: 01 ROUTINE 02 PROBLEM

WHEN: _____ DATE: __/__/__

WHERE: _____

EXPLAIN PROBLEM: _____

DISCHARGE DATE ____/____/____ OR

TRANSFERRED TO _____ SERVICE/HOSPITAL

REASON_____

CURRENT INFORMATION COMPLETED PER ONTOGENY
PHONE NO.
ADDRESS
CITY/STATE/ZIP

ATTENDING FACULTY _____ ,M.D

RESIDENT _____ ,M.D.

UABF03 12/14/90

PS-9654

UAB SCHOOL OF MEDICINE

Department of Obstetrics and Gynecology

June 27, 2000

Waldemar A. Carlo, M.D.
Director, Division of Neonatology
Department of Pediatrics
University of Alabama at Birmingham
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233

RE: Support for the NICHD Cooperative Multicenter Neonatal Research Network

Dear Dr. Carlo:

You and your Division have the unequivocal support of our Division for your Neonatal Network protocols. Our Division has decades of proven clinical and research collaboration with multicenter and single center studies at UAB. Our data systems, especially the OBAR (Obstetric Automated Research System), are integrated with combined prenatal, delivery, postpartum, and neonatal data summaries. We provide combined conferences, research seminars, and collaborate on post-graduate courses for the State of Alabama. Despite our participation in the MFMU Network, there have not been conflicts in patient enrollment in large part because of our periodic meetings between the PIs and research coordinators of the Neonatal and MFM staff. We anticipate continued close clinical and research collaboration and can absolutely guarantee divisional support for your Cooperative Multicenter Neonatal Research Network protocols.

Sincerely,

William Andrews, Ph.D., M.D.
Professor, University of Alabama at Birmingham
Director, Division Maternal-Fetal Medicine

Division of Maternal and Fetal Medicine
Old Hillman Building
618 20th Street South

The University of
Alabama at Birmingham
Mailing Address:
OHB 4FL
619 19TH ST S
BIRMINGHAM AL 35249-7333

DEPARTMENT OF PEDIATRICS
UNIVERSITY OF ALABAMA AT BIRMINGHAM SCHOOL OF MEDICINE
FULL-TIME MEDICAL FACULTY

Child Injury Center
King, William D., Professor

Critical Care Medicine
Tilden, Samuel J., Professor (Division Director)
Buckmaster, Mark A., Assistant Professor
Lemon, Henry, Assistant Professor
Winkler, Margaret K., Associate Professor

General Pediatrics/Adolescent Medicine
Ashworth, Carolyn S., Professor (Division Director)
Miner, Dean, Assistant Professor
Amaya, Michelle I., Assistant Professor
Benton, Cason, Assistant Professor
Evans, H. Hughes, Assistant Professor
Fargason, Crayton A., Associate Professor
Feinstein, Ronald A., Associate Professor
Hoffman, Alisa, Assistant Professor
Nelson, Kathleen G., Professor
Oh, Kim, Professor
Peralta-Carcelen, Myriam, Assistant Professor
Spooner, S. Andrew, Assistant Professor
Stafford, Anne G., Assistant Professor
Sturdevant, Marsha S., Assistant Professor
Thiele, Anne, Assistant Professor
Wall, Terry C., Assistant Professor

Infectious Disease/Virology
Stagno, Sergio, Professor (Department Chair)
Pass, Robert F., (Director)
Britt, William J., Professor
Boppana, Suresh B., Assistant Professor
Crain, Marilyn J., Associate Professor
Sullender, Wayne M., Assistant Professor
Wilson, Craig M., Assistant Professor
Infectious Disease/Clinical Virology
Whitley, Richard J., Professor (Division Director)
Aldrovandi, Grace M., Assistant Professor
Cassady, Kevin, Assistant Professor
Hutto, Cecelia, Assistant Professor
Kimberlin, David W., Assistant Professor

Medical Genetics
Carroll, Andrew (Interim Division Director)
Descartes, Maria D., Assistant Professor
Gregoritch, Jane, Assistant Professor
Han, Jian, Assistant Professor

Neonatology
Carlo, Waldemar A., Professor (Division Director)
Ambalavanan, Namasvayam, Assistant Professor
Coghill, Carl H., Associate Professor
Haywood, James L., Associate Professor
Karle, Virginia A., Assistant Professor
Philips, Joseph B., Professor
Schelonka, Robert, Assistant Professor
St. John, Elaine B., Associate Professor

Pediatric Allergy/Immunology
Hemstreet, Mary Pat, Professor (Division Director)
Atkinson, T. Prescott , Assistant Professor
Hains, Coralie, Associate Professor

Pediatric Cardiology
Colvin, Ed V., Professor (Division Director)
Johnson, Walter, Associate Professor
Lau, Yung R., Assistant Professor
McMahon, William S., Assistant Professor
Pearce, F. Bennett, Associate Professor

Pediatric Emergency Medicine
Glaeser, Peter W., Professor (Division Director)
Baldwin, Steven T., Assistant Professor
Barber, Judson, Assistant Professor
Bernard, David W., Assistant Professor
Embling, Michelle, Assistant Professor
Hardwick, William E., Assistant Professor
Harris, Patricia, Assistant Professor
Klasner, Ann, Assistant Professor
Monroe, Kathy W., Assistant Professor
Nichols, Michele H., Associate Professor
Polhill, Rud B., Associate Professor
Sedlis, James, Assistant Professor

Pediatric Endocrinology
McCormick, Kenneth, Professor (Division Director)
Latif, Hussein, Assistant Professor
Parker, Katrina L., Assistant Professor

Pediatric Gastroenterology/Nutrition
Franklin, Frank A., Professor (Division Director)
Cavender, Cary, Assistant Professor
Guerrero, Roberto A., Assistant Professor

Pediatric Hematology/Oncology
Howard, Thomas H., Professor (Division Director)
Berkow, Roger L., Professor
Castleberry, Robert P., Professor
Hilliard, Lee M., Assistant Professor
May, William A., Assistant Professor
Ship, Alan, Assistant Professor
Watts, Raymond G., Assistant Professor

Pediatric Immunology/Rheumatology
Cooper, Max D., Professor (Division Director)
Atkinson, T. Prescott, Assistant Professor

Pediatric Nephrology
Benfield, Mark R., Associate Professor (Division Director)
Guay-Woodford, Lisa, Associate Professor
Pugh, Judith, Assistant Professor

Pediatric Neurology
Percy, Alan K., Professor (Division Director)
Bebin, Martina, Assistant Professor
Dure, Leon S., Associate Professor
Mussell, Holly, Assistant Professor
Reddy, Alyssa, Assistant Professor
Rutledge, S. Lane, Associate Professor
Teasley, Jean, Assistant Professor
Zachor, Ditza A., Assistant Professor

Pulmonology
Lyrene, Raymond K., Professor (Division Director)
Clancy, John P., Assistant Professor
Grad, Roni, Associate Professor
Hagood, James, Assistant Professor
Makris, Christopher M., Assistant Professor

OTHER FULL-TIME FACULTY AT UAB/THE CHILDREN'S HOSPITAL (Not Directly Under the Chair of Pediatrics)

General Pediatric Surgery
Georgeson, Keith, Professor (Surgeon-in-Chief, Division Director)
Cain, Walter, Professor
Hardin, William Associate Professor
Katz, Douglas, Associate Professor

Pediatric Neurosurgery
Oakes, Jerry, Professor (Division Director)
Grabb, Paul, Assistant Professor
Mapstone, Timothy, Associate Professor

Pediatric Ophthalmology
Kline, Lanning, Professor (Department Chair)
Cogen , Martin, Assistant Professor
Elsas, Fred, Associate Professor
Girkin, Christopher, Assistant Professor
Metz, Thomas, Assistant Professor

Pediatric Orthopedic Surgery
Killian, John, Associate Professor (Division Director)
Conklin, Michael, Assistant Professor
Doyle, J. Scott, Assistant Professor

Pediatric Otolaryngology
Wiatrak, Brian, Associate Professor (Division Director)
Hill, J. Scott, Assistant Professor
Woolley, Audie, Assistant Professor

Pediatric Plastic Surgery
Gardner, Paul Assistant Professor
Grant, John H. Assistant Professor

Pediatric Urology
Joseph David, Professor
Perez, Luis, Assistant Professor

Pediatric Pathology
Kelly, David, Clinical Professor (Pathologist-in-Chief, Medical Director)
Faye-Petersen, Associate Professor
Galliani, Carlos, Clinical Assistant Professor
Mroczek-Musulman, Elizabeth, Clinical Assistant Professor

Pediatric Radiology/Diagnostic Imaging
Royal, Stuart, Professor (Radiologist-in-Chief, Medical Director)
Douglas, Margaret, Clinical Assistant Professor
Frye, Timothy, Clinical Assistant Professor
Guion, Christopher, Clinical Associate Professor
Torgerson, Charles, Clinical Assistant Professor
Vaid, Yoginder, Clinical Professor
Young, Daniel, Clinical Professor

Pediatric Anesthesia
Gutierrez, Juan, Clinical Professor (Anesthesiologist-in-Chief, Division Director)
Brock, Kathryn, Clinical Assistant Professor
Bryant, Paty, Clinical Assistant Professor
Cox, Jerral, Clinical Assistant Professor
Greve, Mark, Clinical Assistant Professor
Laborde, Patricia, Clinical Assistant Professor
Long, Gary, Clinical Assistant Professor
Mackall, Larry, Clinical Assistant Professor
Seigel, Richard, Assistant Professor
Yonfa, Alfonso, Assistant Professor

Child and Adolescent Psychiatry
Asherman, Lee (Division Director)
Dowben, Jonathan, Associate Professor
Belosa, Juan, Associate Professor

Child Behavioral Health
Psychiatrists
Elrefai, Alaa, (Division Director)
Pemmaraju, Rama
Vaughn, Tom
Yoanidis, Nancy
Psychologists
Barnes, Donna
Brooks, Jodene
Patterson, Debra

UAB SCHOOL OF MEDICINE

Department of Pediatrics

May 26, 2000

Waldemar A. Carlo, M.D.
Professor of Pediatrics
Director, Division of Neonatology
The University of Alabama at Birmingham
New Hillman Building – 525
619 South 20th St.
Birmingham, AL 35294

Dear Wally:

It is with great pleasure that I provide this letter of support for your application to participate in the Multicenter Neonatal Research Network sponsored by the National Institute of child Health and Human Development. Obviously, I will do anything in my power to support your application and ensure effective collaboration between members of the Department, the division of Neonatology and work being performed in collaboration with the Department of Obstetrics and Gynecology.

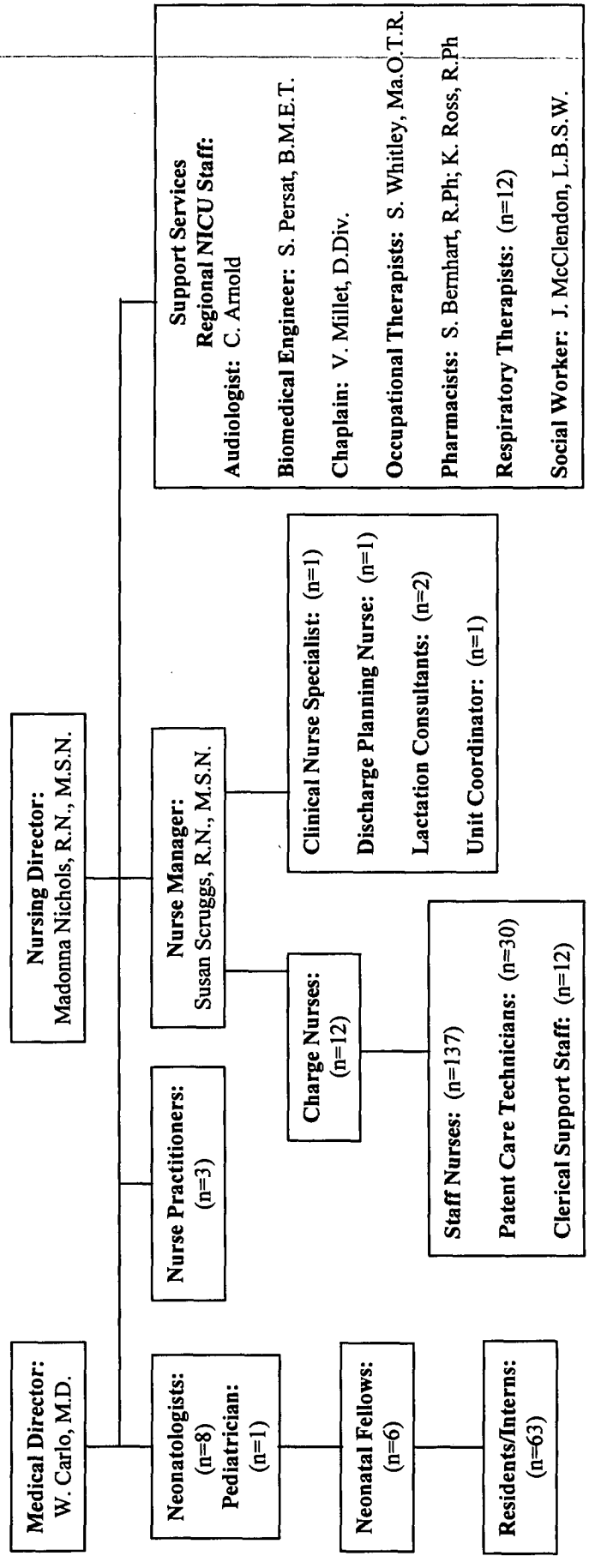
Sincerely yours,

Richard J. Whitley, M.D.
Loeb Eminent Scholar Chair in Pediatrics
Professor of Pediatrics, Microbiology & Medicine

Division of Clinical Virology
616 Ambulatory Care Center
1600 7th Avenue South
205.934.5316
Fax 205.934.8559

The University of
Alabama at Birmingham
Mailing Address:
ACC 616
1600 7TH AVE S
BIRMINGHAM AL 35233-1711

REGIONAL NEONATAL INTENSIVE CARE UNIT AT UAB
ORGANIZATIONAL CHART



HOSPITAL LABORATORIES

Main Laboratory
Anatomic Pathology Laboratory
Arterial Blood Gas Laboratories
Autopsy
Bacteriology Laboratory
Bedside Testing Laboratory
Blood Bank
Bone Marrow Laboratory
Bronchoscopy Laboratory
Cell Identification Laboratory
Chemistry Laboratory
Client Services
Coagulation Laboratory
Cytology Laboratory
Decedent Affairs
Diagnostic Molecular Biology Laboratory
Endo/Toxo Laboratory
GI Laboratory
Hematology Laboratory
Histology Laboratory
Immune Cytopenia Laboratory
Immunology Laboratory
Kirklin Specimen Receiving Laboratory
Kirklin Laboratory
Laboratory Information System
Microbiology Laboratory
Outreach Laboratory
Pulmonary Function Laboratory
Referred Testing Laboratory
Satellite Laboratory
Special Procedures Laboratory
Specimen Receiving Laboratory
STAT Laboratory
Transcription Laboratory
University Emergency Department Laboratory

UAB SCHOOL OF MEDICINE

Medical Student Services

June 26, 2000

Waldemar Carlo, M.D.
Professor of Pediatrics
Director, Division of Neonatology
Director, Newborn Nurseries
525 NHB

Dear Wally:

This is to inform you that we will continue to do the follow-up of infants ≤ 1,000 grams, as part of the "Cooperative Multicenter Network of Intensive Care Units."

As you are aware, I have been the Director of the Follow-up Program for the Neonatal Intensive Nursery since 1977, and I am very proud of the multidisciplinary team that we have assembled to provide follow up services for infants with selected high-risk conditions. In particular, we care for all infants with birthweights ≤ 1,000 grams, all ECMO graduates and selected others, including infants with neonatal seizures and survivors of the surfactant clinical trials. Our clinics at present meet twice weekly, and we have a full time coordinator who has formed close personal relationships with our patients, as well as primary care providers. The communication that we provide both to families and to primary care providers has enabled us to see over 90% of all infants eligible for our services. We have physical assessments, audiological and visual evaluations, in addition to nutritional and social examinations. I am very happy to continue working with you and the rest of the Network Follow-up Program in developing and carrying out follow up protocols for infants cared for in the multicenter center network studies.

On a personal level, I have been very pleased with our professional interactions, both with regard to the Follow-up Program and the support that you have given through the participation of neonatology fellows, and in the normal newborn nursery where my Division has worked very well in an attending capacity. I have worked closely with other members of the Neonatology Division, specifically Drs. Haywood and St. John as well as with you in our AHCPR PORT activities. Because of the collaborative efforts of the Divisions of General Pediatrics, and Neonatology as well as the Department of OB/GYN, especially the Division of Maternal and Fetal Medicine, I believe that we have made major contributions to the understanding of the etiology and prognosis for preterm birth, as well as some in roads into strategies to prevent morbidity and mortality. I look forward to continuing our collaboration over the next years.

Sincerely,

Kathleen G. Nelson, M.D.
Associate Dean for Students
Professor of Pediatrics

P-100 Volker Hall
1670 University Boulevard
205.934.2330
Fax 205.934.8724
www.uab.edu/uasom/mss

The University of
Alabama at Birmingham
Mailing Address:
VH P-100
1530 3RD AVE S
BIRMINGHAM AL 35294-0019

UAB CIVITAN INTERNATIONAL RESEARCH CENTER

Office of the Directors

June 26, 2000

Waldemar A. Carlo, M.D.
Professor and Director
Neonatal/Perinatal Medicine
525 New Hillman
620 South 20th Street
Birmingham, Alabama 35294

Dear Dr. Carlo:

You and your Division have my unequivocal support for your competitive renewal of the National Institutes of Child Health and Human Development's "Cooperative Multicenter Network of Neonatal Intensive Care Units." As head of the special follow-up clinics for infants with disabilities and Director of the Civitan International Research Center, I anticipate a close clinical and research collaborative relationship during the proposed project. I would like to continue pursuing together research opportunities for developmental intervention, such we did recently in our pilot of educational intervention in high and low risk preterm infants.

Sincerely,

Craig T. Ramey

Craig T. Ramey, Ph.D.
Director and Professor
Psychology, Pediatrics, Public
Health Sciences and Sociology

The University of Alabama at Birmingham
SC 313
Birmingham, Alabama 35294-0021 • (205) 934-8900 • FAX (205) 975-6330

SPECIAL DEVELOPMENTAL DISABILITIES CLINICS
CIVITAN INTERNATIONAL RESEARCH CENTER

The Sparks Clinics complex is a major site for clinical research programs at the Civitan International Research Center. An extensive range of interdisciplinary clinics provides comprehensive diagnosis, and evaluation, and treatment of the needs of children and adults with mental retardation and developmental disabilities. Each of the Sparks Clinics consults with clients in a context that considers the unique needs of individuals and their family members.

The strength of the Center's interdisciplinary approach to delivering services is clearly evident in the Sparks Clinic. Faculty, students, and staff, representing many different disciplines, apply their skills in a collaborative manner, ensuring that clients receive state-of-the-art evaluations and well-rounded assessments of their individual needs. Some of the clinical research and service programs at the Civitan International Research Center that provides evaluations to the graduates of the NICU include:

Audiology Clinic - Provides evaluations for assessing hearing impairment in children with developmental disabilities. Assists in fitting and dispensing hearing aids and assistive listening devices.

Augmentative Communication and Assistive Technology Clinic - Provides assessments for children who are functionally nonspeaking in addition to having physical, cognitive, and sensory problems. Offers technical assistance to families, professionals, schools and community agencies regarding communication needs, including sign language, communication boards, electronic voice output devices, as well as a range of assistive instruments, such as personalized switches and computers.

Child Developmental Clinic - Specializes in evaluations of children 3-7 years, whose development, learning, or behavior cause concern. Members of an evaluation team, composed of social workers, pediatricians, and other specialized clinicians evaluate and recommend medical, social, psychological, and educational interventions.

Child Find Clinic - Evaluates infants and toddlers who have or who are at risk for developmental problems. Family support information is an important aspect of the services provided through this clinic.

Child and Adolescent Behavior Clinic - Offers services to children who have developmental disabilities and exhibit behavior or emotional problems. Other services include short-term parent training, psychiatric consultation and medication follow-up.

Comprehensive Child Development Program - Creates innovative programs for children and families affected by substance abuse.

Dental Clinic - Provides routine and specialized dentistry services for children with mental retardation and developmental disabilities. Offers consultations and evaluations of oral health as needed by other clinics.

Inborn Errors of Metabolism Clinic - Provides evaluation following diagnosis of infants and children with PKU (phenylketonuria), galactosemia, and other rare inborn errors of metabolism. Offers medical nutritional, educational assistance to these individuals and their families.

Multiple Disabilities Clinic - Provides diagnosis and recommends treatment for patients who have one or more disabling conditions, such as spina bifida, cerebral palsy, speech/language disorders, genetic disorders, and vision or hearing disabilities. The clinic team evaluates disorders and develops recommendations and plans to meet client and family needs.

Neurology Clinic - Evaluates and treats children from birth to 18 years who have disorders of the nervous system due to developmental delay. This disorders include seizures, Rett and Tourette Syndromes, epilepsy, static encephalopathy, and disorders related to Huntington disease and dystonias.

Nutrition Clinic - Assesses and evaluates children with disabilities diagnosed with feeding and eating problems.

Optometry Clinic - Provides vision examination, refraction, and treatment services for children and adolescents with disabilities.

Occupational Therapy Clinic - Evaluates, assesses, and treats children with physical, emotional, and developmental deficits. Services focus on fine motor skills, visual perception, sensory processing, organizational skills, overall smooth, coordinated and purposeful movement, and other activities of daily living.

Physical Therapy Clinic - Develops assessment and therapy plans for individuals with physical, emotional, and developmental disabilities.

Psychoeducational Clinic - Evaluates school-age children who have academic difficulties that cannot be adequately addressed by local school systems and psychosocial services providers.

Speech and Language Clinic - Provides communication services to individuals who have developmental disorders from birth through adulthood.

PEDIATRIC SPECIALTY CLINICS

Adolescent Clinics
General Adolescent
Hyperactivity
Teen Accent
Teen Health
Teen Tot

Endocrinology Clinics
Diabetic
General Endocrinology

Hematology/Oncology Clinics
Hematology
Infusion Therapy
Neuro-Oncology
Oncology
Sickle Cell

Neurology Clinics
Epilepsy
General Neurology
Muscular Dystrophy

Orthopedic Clinics
Fracture
General Orthopedics
Hand

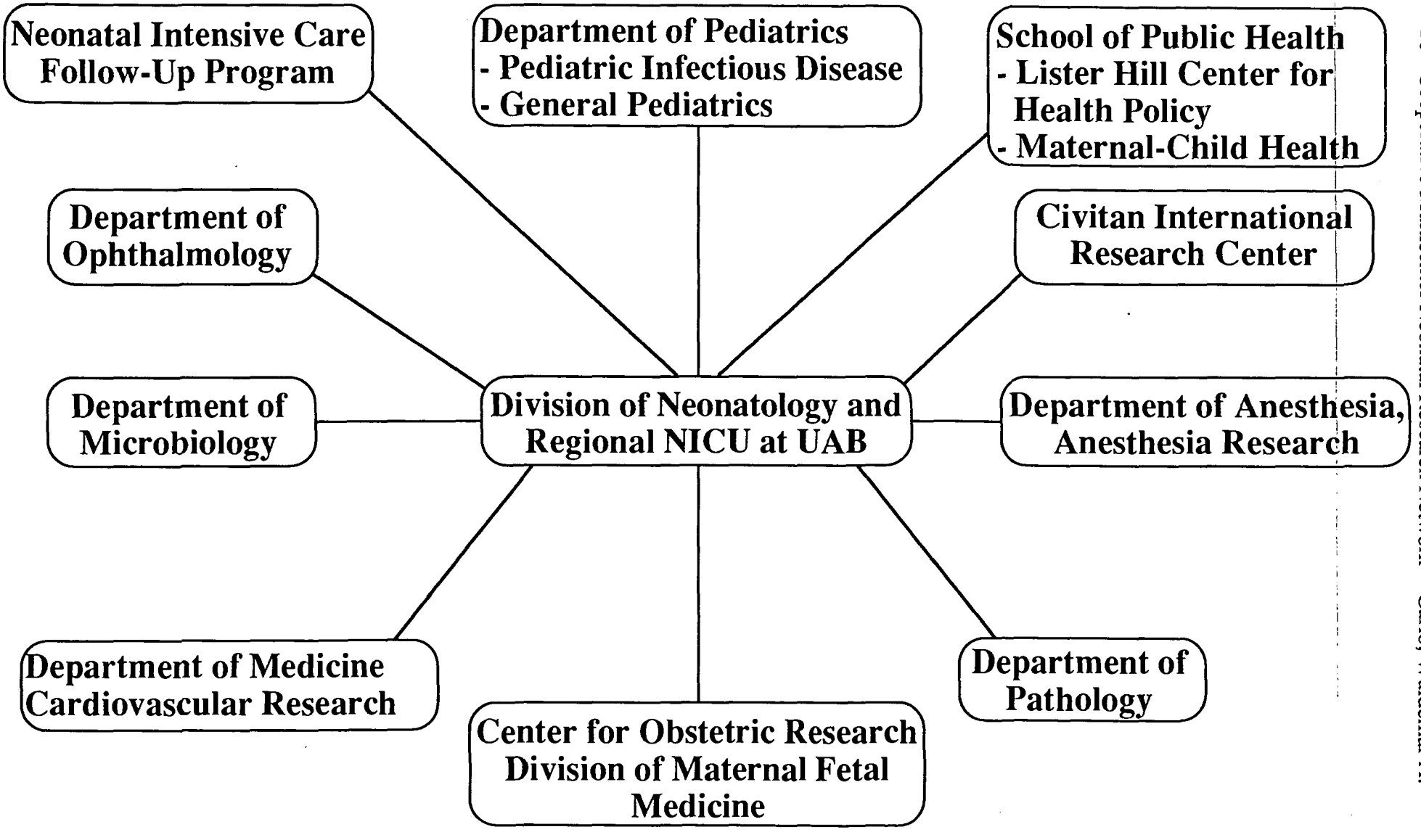
Primary Care Clinics
Primary Care (Resident's clinic)
General Pediatrics

Surgical Clinics
Burns
Cranio-Facial/Cleft Palate
ENT
General Surgery
GU
Gynecological
Neurosurgery
Plastic Surgery
Spina Bifida
Suture Removal

Pulmonary Clinics
Cystic Fibrosis
General Pulmonary

Other Specialty Clinics
Allergy
Cardiology
Down's Syndrome
Gastroenterology
Genetics
Immunology
Infectious Disease
Newborn Follow-up
Nutrition Support
Renal

Research Collaborations of the Division of Neonatology/Regional NICU at UAB



UAB SCHOOL OF MEDICINE

James A. Pittman General Clinical Research Center

June 28, 2000

Waldemar Carlo, M.D.
Director, Division of Neonatology
Director, Newborn Nurseries
The University of Alabama at Birmingham
525 New Hillman Building
Birmingham, AL 35233-7335

Dear Dr. Carlo:

On behalf of the Pittman General Clinical Research Center at the University of Alabama, it is my pleasure to write this letter of support regarding your application to the National Institutes of Health for your grant proposal entitled, "NICHD Cooperative Multicenter Neonatal Research Network". We have recently occupied a new 12,694 square foot General Clinical Research Center facility on the ninth floor of the Medical Education Building, which will better address your clinical research needs. We are pleased that you continue to utilize the GCRC in your studies.

I wish you success in receiving funding for this grant. At the time it is awarded, we will work with you in our usual manner to schedule these patients. Please let me know how I can be of further assistance in your application process.

Sincerely,

Larry W. Moreland /lz

Larry W. Moreland, M.D.
Director

LWM:chp

M907 Medical Education Building
1813 6th Avenue South
205.934.4852
Fax 205.975.6616

The University of
Alabama at Birmingham
Mailing Address:
MEB M907
619 19TH ST S
BIRMINGHAM AL 35249-6909

Neonatal Database Data Collection Form

Keyplate

Bold boxed areas cannot be left blank. Data outside field limits will be rejected. Please double check written all written entries prior to submission for computer entry. Enter all times using 24 hr clock.

IDENTIFYING INFORMATION

Last Name: _____ First Name: _____

Sex: ☐ Race: ☐ _____ Baby MR #: _____ Admit Dx: _____

M/F/Unk. B/W/Other *(specify)* *As recorded in logbook*

Birth Date: _____ Admit Date: _____ Admit Date: _____

Birth Time: _____ Admit Time: _____ Admit Time: _____

Birth Hospital: _____ Disch. Site: _____ Disch. Site: _____

Disch. Date: _____ Disch. Date: _____

Referral status: ☐
1. UAB
2. Fetal Referral
3. Outborn

Admit Date: _____ Admit Date: _____

Admit Time: _____ Admit Time: _____

Disch. Site: _____ Disch. Site: _____

Disch. Date: _____ Disch. Date: _____

Mom's Name: _____

Mom's MR #: _____

Address: _____

Phone #: _____

County: _____

Mother's Residence; "NA" if outside Alabama

Computer will total length of stay and record as separate field

MATERNAL HISTORY, BIRTH HISTORY, PHYSICAL EXAM

If maternal history not available on outborn infants record "NA"

Mat. Age: _____

GA wks (OB Best Est.): ☐

Hypertension: *(any form)* ☐ Yes ☐ No

Mat. Infection: *(OB clinical Dx.)* ☐ Yes ☐ No

Abx prior to Del.: *(within 48hrs)* ☐ Yes ☐ No

Placental Separation: ☐ Yes ☐ No

Maternal Diabetes: ☐ Yes ☐ No

Class: ____

Subst. Abuse: ☐

0. None
1. Tobacco
2. Alcohol
3. Marijuana
4. Cocaine
5. Narcotics
6. Other

Syphilis ☐ Pos ☐ Neg ☐ Unk

HBSAg ☐ Pos ☐ Neg ☐ Unk

HIV ☐ Pos ☐ Neg ☐ Unk

GBS ☐ Pos ☐ Neg ☐ Unk

ROM (hrs): ____

Betamimetics ☐ Yes ☐ No

Steroids ☐ Yes ☐ No

Indomethacin ☐ Yes ☐ No

MgSO4 ☐ Yes ☐ No

# of Births: ☐

Birth Order: ☐

Apgars 1': ____ 5": ____ 10": ____

Cord pH(art): _____

CSection: ☐ Yes ☐ No

Indication: ☐

1. Fetal Intolerance to Labor
2. Abnormal Presentation
3. Other Fetal Indication
4. Hypertension
5. Previous C/S
6. Failure to Progress
7. Other Maternal Indication
8. Unknown

Birth Wgt. (g): ☐

Ballard: _____wks

AGA / SGA / LGA *(circle one)*

Head Circ: _____ cm

Length: _____ cm

Fetal Distress ☐ Yes ☐ No

Meconium ☐ Yes ☐ No

Peds at Delivery ☐ Yes ☐ No

Bag & Mask Resus. ☐ Yes ☐ No

Laryngoscopy *(suction)* ☐ Yes ☐ No

Intubation *(Ventilation)* ☐ Yes ☐ No

Birth Trauma ☐ Yes ☐ No

Dysmorphic Facies ☐ Yes ☐ No

Structural Anomalies ☐ Yes ☐ No

Chromosomes: ☐

1. Not Tested
2. Normal
3. Abnormal
4. Unknown

ORGAN SYSTEMS

TTN ☐ Yes ☐ No

HMD ☐ Yes ☐ No

BPD (O_2 at 28 days) ☐ Yes ☐ No

PIE ☐ Yes ☐ No

Pulm. Hemorr. ☐ Yes ☐ No

Airblock ☐ Yes ☐ No

Pneumonia ☐ Yes ☐ No

Apnea ☐ Yes ☐ No

Mec. Asp ☐ Yes ☐ No

Other Lung Dz. ☐ Yes ☐ No

O_2 days: ☐

IMV days: ☐

Hi Freq ☐ Yes ☐ No

NCPAP ☐ Yes ☐ No

NCPAP+IMV ☐ Yes ☐ No

Surfacant ☐ Yes ☐ No

Paralysis ☐ Yes ☐ No

Aminophylline ☐ Yes ☐ No

Steroids ☐ Yes ☐ No

PDA ☐ Yes ☐ No

Cong.Heart ☐ Yes ☐ No

Type: _____

PPHN ☐ Yes ☐ No

Failure ☐ Yes ☐ No

Arrythmia ☐ Yes ☐ No

IV Inotropes ☐ Yes ☐ No

Digitalis ☐ Yes ☐ No

Echo ☐ Yes ☐ No

CVSurg. ☐ Yes ☐ No

PGE ☐ Yes ☐ No

ECMO ☐ Yes ☐ No

Tolazoline ☐ Yes ☐ No

Diuretics ☐ Yes ☐ No

Proph. Indocin ☐ Yes ☐ No

Rescue Indocin ☐ Yes ☐ No

IVH ☐ Yes ☐ No

Max. grade: _____

PVL ☐ Yes ☐ No

Other Abnl'ty ☐ Yes ☐ No

Seizures ☐ Yes ☐ No

Cranial U/S: ☐

Therapeutic LP ☐ Yes ☐ No

Neurosurg. ☐ Yes ☐ No

CT Head ☐ Yes ☐ No

EEG ☐ Yes ☐ No

Fdg. Intol. ☐ Yes ☐ No

NEC ☐ Yes ☐ No

Bell stage: _____

Date Full Fdgs: _____

Cholestasis ☐ Yes ☐ No

Perforation ☐ Yes ☐ No

GI Surg. ☐ Yes ☐ No

TP Tube ☐ Yes ☐ No

Gastrostomy ☐ Yes ☐ No

Insulin ☐ Yes ☐ No

TPN days: _____

Hemol. Dis. ☐

0. None
1. ABO
2. Rh
3. Other

Max.Bili.Total: _____

Max. Bili. Dir.: _____

Max.Bili.Indir.: _____

Phototherapy ☐ Yes ☐ No

Coagulopathy ☐ Yes ☐ No

Platelets < 100k ☐ Yes ☐ No

ANC < 1250 ☐ Yes ☐ No

PRBC Tx.: _____

Whole Blood Tx.: _____

Exchange Tx.: _____

Plasma Tx.: _____

Platelet Tx.: _____

Renal Failure ☐ Yes ☐ No

GU Abnormality ☐ Yes ☐ No

Highest Sodium _____ Date _____ Time _____

Lowest Sodium _____ Date _____ Time _____

Highest Glucose _____ Date _____ Time _____

Lowest Glucose _____ Date _____ Time _____

GENERAL PROCEDURES

UAC ☐ Yes ☐ No

UVC ☐ Yes ☐ No

Periph. Art.Line ☐ Yes ☐ No

Central Line ☐ Yes ☐ No

CPR Drugs ☐ Yes ☐ No

CPR, Compressions ☐ Yes ☐ No

INFECTIOUS DISEASE

Positive Cultures

Date	Site	Organism(s)				
Serology						
Syphilis ☐ Yes ☐ No						
Toxo ☐ Yes ☐ No						
Rubella						
HIV ☐ Yes ☐ No						
Hep. B ☐ Yes ☐ No						

Antibiotic Courses

Drug	Start Date	#Days

SITES:
01 Central Line
02 Skin
03 Tracheal Asp
04 Peritoneal tap
05 Wound
06 Stool/Rectal
07 Umbilicus
08 Nasopharynx
09 Conj/Eye
10 Blood
11 CSF
12 Urine
13 Other

ORGANISMS:
01 Strep B
02 Strep Viridans
03 Strep D/Enterococcus
04 Other Strep
05 Staph Aureus
06 Staph Epi
07 Micrococcus/Other Staph.
08 E. Coli
09 Klebsiella
10 Enterobacter
11 Serratia
12 Citrobacter/Arizona/Edwardsiella
13 Providentia/Erwinia
14 Pseudomonas
15 Shigella/Salmonella/Proteus
16 Haemophilus
17 Listeria
18 Acinetobacter/Nima/Herella
19 Bacteroides
20 Aeromonas
21 Mycoplasma
22 Ureaplasma
23 Other Bacterial
24 CMV
25 Herpes
26 Rotavirus
27 Other Virus
28 Candida
29 Other Fungus

ANTIBIOTICS:
01 Penicillin
02 Ampicillin
03 Meth/Nafcillin
04 Cephalosporin
05 Aminoglycoside
06 Vancomycin
07 Erythromycin
08 Other
09 Local

STATUS AT DISCHARGE

(Last discharge date above)

Disch. Wgt. (g): ☐

Hearing: ☐
1. Not Tested
2. Normal
3. Abnormal
4. Unknown

ROP screen: ☐
1. Not Tested
2. Normal
3. Abnormal*
4. Unknown

*Stage:____ Zone:____
(Highest grade)

FollowUp Site: _____
(Dr.'s name or Health Dept. Clinic)

Study Participation *(list)*: _____

_____

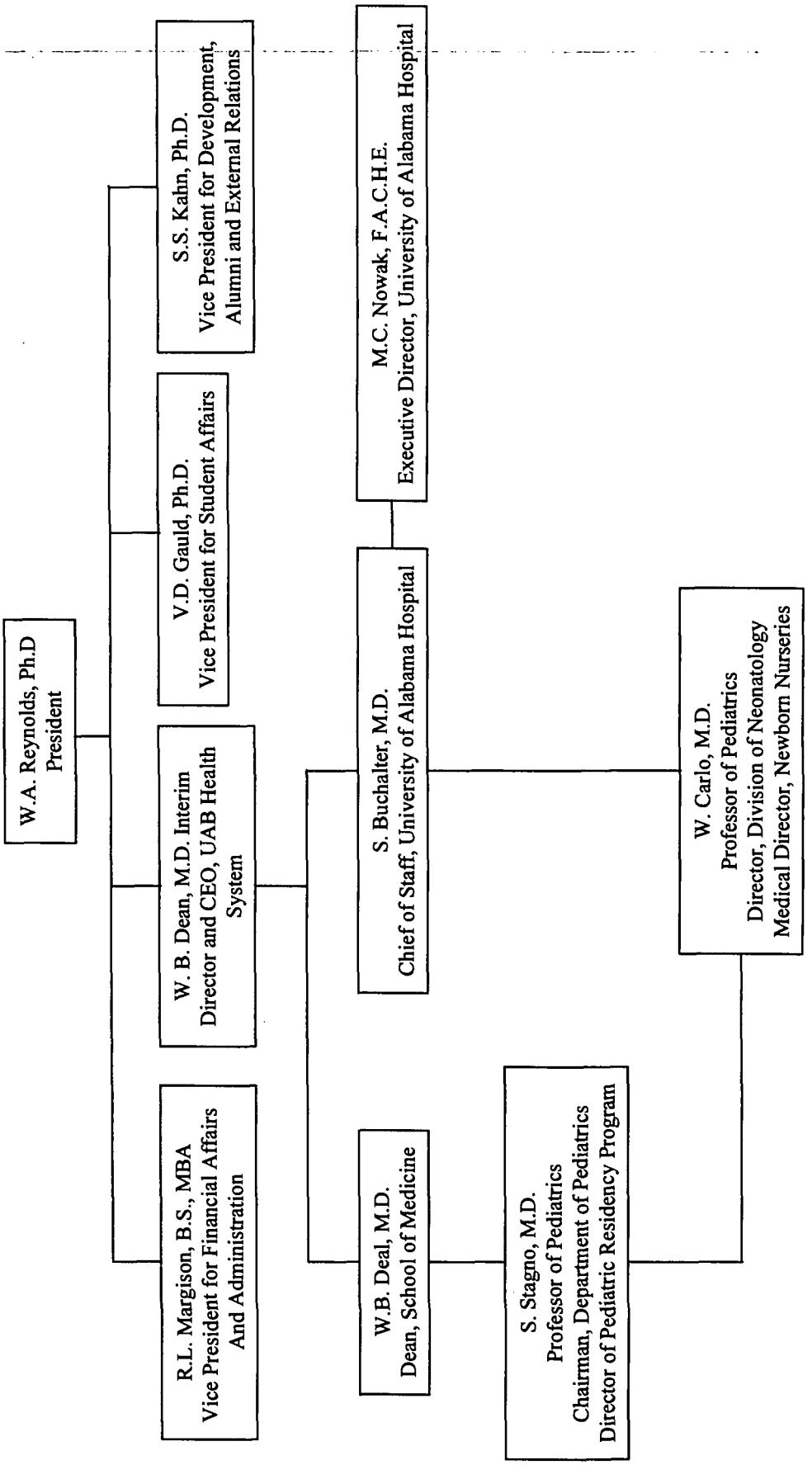
Died ☐ Yes ☐ No

Date Died: _____

Time Died: _____

Autopsy Yes / No *(circle)*

UNIVERSITY OF ALABAMA AT BIRMINGHAM – UNIVERSITY OF ALABAMA HOSPITAL
ORGANIZATIONAL CHART



UAB SCHOOL OF MEDICINE

Office of the Dean

June 26, 2000

Waldemar A. Carlo, M.D.
University of Alabama at Birmingham
Division of Neonatology
619 South 20th Street
Birmingham, AL 35233

RE: University of Alabama at Birmingham's application in response to HD 00-010 "Cooperative Multicenter Neonatal Research Network"

Dear Dr. Carlo:

Thank you for sharing with me your commitment to reapply for the Neonatal Research Network grant. The interests and accomplishments of your Division over the years provide convincing evidence of the capabilities for neonatal clinical research projects here at UAB. The unique opportunities afforded in clinical neonatology to work across Division and Department lines and to foster multidisciplinary research has been ably realized by our activities in the Division of Neonatology over the past years.

The University of Alabama School of Medicine, UAB, has been and continues to be committed to the support of excellence in clinical research. The activities of most departments in this institution reflect this emphasis in their activities and publications. The tradition established by years of excellence in the care of newly born infants, as well as the role of pediatrics and neonatology here at UAB as leader in regional planning within this state and southeastern region provide added evidence of UAB's capability to serve as a national center for clinical trials. It is of particular interest to me to realize how closely the words of the RFA for this neonatal network echo so closely our efforts at the University, as well as the need is for clinically relevant, properly designed, hypothesis-testing scientific trials in neonatology.

The University of Alabama at Birmingham understands and agrees to the demands of the "Cooperative Agreement." The special requirements entailed in cooperative agreement will be met in a timely and efficient manner. UAB is dedicated to supporting the academic achievement of our programs and feels the participation of our faculty in a network will be mutually beneficial and stimulating. Certainly, your application has my total enthusiastic and unqualified support. Success would be well earned based on the past accomplishments in neonatology here and would further strengthen the already excellent programs in this field at the University of Alabama School of Medicine, UAB.

Sincerely,

William B. Deal, M.D.
Dean

cc: Sergio B. Stagno, M.D.

306 Medical Education Building
1813 6th Avenue South
205.934.1111
Fax 205.934.0333

The University of
Alabama at Birmingham
Mailing Address:
MEB 306
1530 3RD AVE S
BIRMINGHAM AL 35294-3293

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UAB SCHOOL OF MEDICINE

Department of Pediatrics
Office of the Chairman

June 27, 2000

Waldemar A. Carlo, M.D.
Department of Pediatrics
Division of Neonatology
University of Alabama at Birmingham
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233

Dear Wally:

I am pleased that you are reapplying for the National Institute of Child Health and Development RFA "Cooperative Multicenter Research Network." As in the past I am firmly committed to support you for what I consider to be a very exciting research opportunity.

In my opinion, you and your Division are ideally suited to conduct and direct the type of investigations being proposed. You certainly have an outstanding record, both as a leader in the field of Neonatology, and as Principal Investigator with the Network with vast experience in collaborative studies. This includes the relationship with Dr. Robert Goldenberg and his associates on the Low Birthweight PORT and the PERC studies. The success of this and your outstanding experience with the Network clearly attest to the fact that you have the ability to work well with others and bring the full resources of your Division into play in the conduct of such investigations.

I am convinced that such an approach as you now envision is the only way to obtain meaningful answers to critical questions. Certainly, your ability to provide the leadership that our participation in this Network would require has been amply demonstrated. You also have the much needed experience and understanding that comes from you serving as a leader and consultant to various agencies and organizations concerned with Neonatology.

Finally, UAB, the Department of Pediatrics, and your own Division have an excellent reputation as leaders in clinical and basic science research. I am pleased to continue to commit the necessary support in the areas of administration, personnel management and space allocation to ensure your success. The administrative staff of the Department will provide support as needed to comply with all necessary policies and budget management. As in previous years, we cooperate fully with the policy of capitation of research costs.

Please let me know if I can be of further help.

Sincerely,

Sergio Stagno, M.D.
Katharine Reynolds Ireland
Professor and Chairman
Department of Pediatrics

The University of Alabama at Birmingham
600 Ambulatory Care Center • Children's Hospital • 1600 Seventh Avenue South
Birmingham, Alabama 35233-0011 • (205) 934-4280 • FAX (205) 939-9977

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Provost Office

June 27, 2000

Waldemar A. Carlo, M.D.
Department of Pediatrics
Division of Neonatology
University of Alabama at Birmingham
619 South 20th Street
525 New Hillman Building
Birmingham, AL 35233

Dear Dr. Carlo:

I've reviewed your reapplication for the National Institute of Child Health and Development RFA "Cooperative Multicenter Research Network." As in the past, UAB is committed to providing the support necessary for your research to continue.

The University of Alabama at Birmingham has an excellent reputation as a leader in clinical and basic science research. I am pleased to continue to commit the necessary support in the areas of institutional review, pre and post award administration, required research space and necessary infrastructure. As in previous years, we cooperate fully with the policy of capitation of research costs.

Please let me know if I can be of further help.

Sincerely,

Joan F. Lorden, PhD
Associate Provost for Research
University of Alabama at Birmingham

Office of Grants and Contracts Administration
1170 Administration Building
701 20th Street South
205.934.5266
Fax 205.975.5977

Mailing Address:
AB 1170
1530 3RD AVE S
BIRMINGHAM AL 35294-0111

AA

UCSD # 20-7545

Form Approved Through 2/28/01

OMB No. 0925-0001

Department of Health and Human Services

6 9 1 8 2 7

vice

5 a t U b b 1 1 2 1

PI: **FINER, NEIL**

Council: 01/2001

Grant #: 1 U10 HD040461-01

Dual:

IRG: ZHD1 SRC(99)

Received: 07/11/2000

Follow instructions carefully.
Do not exceed character length restrictions indicated on sam

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spac*

Cooperative Multicenter Neonatal Research

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [ ] NO [X] YES *(If " Yes," state number and title)*

Number: HD-00-010 Title: Cooperative Multicenter Neonatal Research Network

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR New Investigator [X] YES

3a. NAME *(Last, first, middle)*
Finer, Neil N.

3b. DEGREE(S)
M.D.

3d. POSITION TITLE
Professor

3e. MAILING ADDRESS *(Street, city, state, zip code)*
UCSD Medical Center
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Pediatrics/Neonatology

3g. MAJOR SUBDIVISION
School of Medicine

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 619-543-3759
FAX: 619-543-3812

E-MAIL ADDRESS:
nfiner@ucsd.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date	Full IRB or Expedited Review	4b. Assurance of compliance no.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	5b. Animal welfare assurance no.
[ ] No [X] Yes	Pending	[ ]	M1274	[X] No [ ] Yes		

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
04/01/01	03/31/06	134,952	202,907	714,317	1,084,036

9. APPLICANT ORGANIZATION

Name **The Regents of the Univ. of Calif.**
Address **Univ. of Calif., San Diego**
9500 Gilman Drive, 0934
La Jolla, CA 92093-0934

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [X] State [ ] Local
Private: → [ ] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE **01**

12. ENTITY IDENTIFICATION NUMBER **1956006144A1**
DUNS NO. (if available) **80-435-5790**
Congressional District **49**

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE

Name Jean Linder
Title **Contract & Grant Officer**
Address **Ofc. of Contract & Grant Admin.**
Univ. of Calif. , San Diego
9500 Gilman Drive, 0934
La Jolla, CA 92093-0934

Telephone **(858) 534-0244**
FAX **(858) 534-0280**
E-Mail **nihawds@ocga.ucsd.edu**

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION

Name **Colleen M. Carpenter**
Title **Director SOM C&G Office**
Address **School of Medicine**
Univ. of Calif., San Diego
9500 Gilman Drive, 0602
La Jolla, CA 92093-0602

Telephone **(858) 534- 3202**
FAX **(858) 534-6573**
E-Mail **ccarpent@ucsd.edu**

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per " signature not acceptable.)*

Neil Finer

DATE: 6/30/00

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per " signature not acceptable.)*

Colleen M. Carpenter

DATE: 7/6/2000

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

As part of its continuing commitment to improve the care and outcome of both premature and full term infants requiring neonatal intensive care, the Division of Neonatology at the UCSD Medical Center is applying to join the NICHD Neonatal Research Network. The core neonatal faculty of UCSD provides clinical care, performs both clinical and applied research, and has an active training program in newborn medicine. The principle nursery is at the UCSD Medical Center in Hillcrest, a 40-bed regional care NICU with approximately 560 admissions of which approximately 82% of admissions are inborn. We have developed a consortium relationship with Sharp Mary Birch Hospital for Women (SMBHW), currently the largest delivery hospital in California, which admitted 1112 infants in 1999. SMBHW has committed to hiring a full-time neonatal research nurse to facilitate their participation in the Research Network. Both neonatal units are members of the National and State Neonatal Databases which include the Vermont Oxford Network (VON) and the California Perinatal Quality Care Collaborative (CPQCC). UCSD and SMBHW have active maternal-fetal medicine programs with ongoing collaboration between the Perinatal and Neonatal programs. Our neonatal programs have significant experience in multicenter prospective randomized trials, and observational studies and are committed to the ongoing critical evaluation of all aspects of care provided to critically ill neonates. The UCSD School of Medicine is committed to the support of prospective clinical research and has unique expertise in pharmacokinetics, microbial pathogenesis, biochemical genetics and dysmorphology and teratology which would enhance the activity of the Neonatal Network. We offer a large unique, ethnically diverse population of both very low birthweight and near-term and term infants and an experienced and committed faculty for participation in prospective randomized clinical trials and enthusiastically seek membership participation in the Neonatal Research Network.

PERFORMANCE SITE(S) *(organization, city, state)*

University of California, San Diego Medical Center—Hillcrest, Infant Special Care Center, San Diego, CA
Sharp Mary Birch Hospital for Women, Neonatal Intensive Care Unit, San Diego, CA

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Neil N. Finer, M.D.	UCSD, Department of Pediatrics	Principal Investigator
Graham Bernstein, MD	Sharp Mary Birch Hospital for Women/UCSD	Co-Investigator
Deirdre Browner, M.P.H.	UCSD, Department of Pediatrics	Data Manager
Edmund Capparelli, Pharm.D.	UCSD Department of Pharmacology	Consultant
Val Catanzarite, M.D., Ph.D.	Sharp Mary Birch Hospital for Women	Consultant
Gregory Heldt, M.D.	UCSD, Department of Pediatrics	Co-Investigator
Frank Mannino, M.D.	UCSD, Department of Pediatrics	Co-Investigator
Ellen Milan, R.N.C.	UCSD, Department of Pediatrics	Research Nurse Coordinator
Thomas Moore, M.D.	UCSD, Department of Reproductive Medicine	Consultant
Yvonne Vaucher, M.D., M.P.H	UCSD, Department of Pediatrics	Co-Investigator
Paul Wozniak, M.D.	Sharp Mary Birch Hospital for Women	Consultant

Type the name of the principal investigator/program director at the top of each printed page and each continuation page. (For type specifications, see instructions on page 6.)

RESEARCH GRANT

TABLE OF CONTENTS

Research Plan

*Type density and type size of the entire application must conform to limits provided in instructions on page 6.

Appendix (*Five collated sets. No page numbering necessary for Appendix.*)
Number of publications and manuscripts accepted or submitted for publication (*not to exceed 10*) _____
Other items (*list*):

☐ Check if Appendix is Included

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 04/01/01 THROUGH 3/31/02

PERSONNEL *(Applicant organization only)* NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Neil Finer	Principal Investigator	#	%	$	14,130.	2,402.	16,532.
Frank Mannino	Co-Investigator				0.	0.	0.
Yvonne Vaucher	Co-Investigator				0.	0.	0.
Gregory Heldt	Co-Investigator				0.	0.	0.
Graham Bernstein	Co-Investigator				0.	0.	0.
Deirdre Browner	Data Manager				12,840.	2,953.	15,793.
Ellen Milan	Nurse Coordinator				57,420.	13,207.	70,627.
*15% effort/10% salary requested							
SUBTOTALS →					84,390.	18,562.	102,952.

CONSULTANT COSTS

Thomas Moore, M.D.
Paul Wozniak, MD
Edmund Capparelli, Pharm.D.
Val Catanzarite, MD, PhD — 0.

Laptop Computer — 3,000. — ~~3,000.~~

SUPPLIES *(Itemize by category)*

Consumable office and computer supplies — 1,200.
Fax machine — 300.

1,500 ~~1,500.~~

TRAVEL

10 trips to Bethesda, MD. @ $2,500/trip — 2,500 ~~25,000.~~

PATIENT CARE COSTS

INPATIENT — None — 0. — 0.
OUTPATIENT — None — 0. — 0.

ALTERATIONS AND RENOVATIONS *(Itemize by category)* — 0.

0. — 0.

OTHER EXPENSES *(Itemize by category)*

Telecommunications ($75/month) — 900. — 0.
Duplication/Printing ($50/mo) — 600. — 0.
Postage/Shipping ($50/mo) — 600. — 0.
Publication Expenses — 400. — 0. — ~~2,500.~~

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD — **$ 134,952.**

CONSORTIUM/CONTRACTUAL COSTS

DIRECT COSTS — 0.
FACILITIES AND ADMINISTRATION COSTS — 0.

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* → **$ 134,952.**

= Months Devoted to Project
% = Percentage of Effort
$ = Institutional Based Salary

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD

DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD *(from Form page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits* *Applicant organization only*	102,952.	106,041.	109,222.	112,498.	115,873.
CONSULTANT COSTS	0.	0.	0.	0.	0.
EQUIPMENT	3,000.	0.	0.	0.	0.
SUPPLIES	1,500.	4,500.	4,500.	4,500.	4,500.
TRAVEL	25,000.	25,750.	26,523.	27,319.	28,139.
PATIENT CARE COSTS — INPATIENT	0.	0.	0.	0.	0.
PATIENT CARE COSTS — OUTPATIENT	0.	0.	0.	0.	0.
ALTERATIONS AND RENOVATIONS	0.	0.	0.	0.	0.
OTHER EXPENSES	2,500.	2,500.	2,500.	2,500.	2,500.
SUBTOTAL DIRECT COSTS	134,952.	138,791.	142,745.	146,817.	151,012.
CONSORTIUM/ CONTRACTUAL COSTS — DIRECT	0.	0.	0.	0.	0.
CONSORTIUM/ CONTRACTUAL COSTS — F & A	0.	0.	0.	0.	0.
TOTAL DIRECT COSTS	134,952.	138,791.	142,745.	146,817.	151,012.

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD *(Item 8a, Face Page)* → $ **714,317.**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Please see following page for budget justification.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Justification

Personnel:

Neil N. Finer, MD will be the Principal Investigator and will supervise all aspects of work related to the NICHD Neonatal Network. The requested salary support represents % effort as stipulated, although NF anticipates contributing at least % of his time to work related to NICHD Neonatal Network.

No salary support is requested for the co-investigators who will be contributing % of their time to work related to the Neonatal Network. Individual co-investigators will be assigned a specific role on individual projects.

Frank Mannino, MD will be a co-investigator involved in relevant clinical trials as a coordinator.

Gregory Heldt, MD will be a co-investigator planning both acute and chronic pulmonary function testing as required by clinical trials.

Yvonne Vaucher, MD, MPH will be a co-investigator assisting in protocol development especially in the areas of (1) study design and statistical evaluation and (2) organization and content of follow-up for clinical trails.

Graham Bernstein, MD will be a co-investigator and supervise clinical trial activity and generic database entry at Sharp Mary Birch Hospital for Women.

Ellen Milan, RNC, the Research Nurse Coordinator, will assist in all aspects of the proposed research. She has extensive NICU nursing experience and has been the neonatal research nurse involved in numerous projects including the antenatal TRH project, Prospective Evaluation of g-CSF and other trials performed in our unit.

Deirdre Browner, BS, MPH, data manager will assist with the management of the database and devote % effort to the NICHD Neonatal Network.

Consultants

No salary support is requested for the consultants who will be contributing their time to work related to the Neonatal Network. Consultants will be assigned a specific role on individual projects.

Thomas Moore, M.D., Professor and Chairman of Reproductive Medicine and Divisional Chief of Maternal Fetal Medicine will be the consultant perinatologist-obstetrician.

Paul Wozniak, MD, Medical Director, Neonatal Services, will be the consultant for administrative support of clinical research and generic data base entry at Sharp Mary Birch Hospital for Women.

Val Catanzarite, MD, PhD, Director, Perinatal Imaging, Sharp Perinatal Center will be the consultant perinatologist at Sharp Mary Birch Hospital for Women.

Edmund V. Capparelli, Pharm.D., Project Pharmacologist will be the consultant for pharmacokinetics-pharmacodynamic evaluation for current and future trials and consultant for potential add-on sub-trials.

% = Percentage of Effort

Equipment:
In year 01, $3,000 is requested for a laptop Sony PCG Z505 JSK VAIO Z505 portable computer with fax modem. With a single coordinator and data entry clerk, this laptop computer is necessary to accomplish data collection in the two NICU sites and to facilitate data transmission to the Network data center.

Supplies:
In year 01, $1,500 is requested for fax machine, consumable office and computer supplies needed to facilitate communication among the NICUs for network-related research. To allow for increased cost as research projects are implemented, this cost is increased to $4500 beginning in year 02.

Travel:
Funds are requested as specified for 10 trips per year for Network team (two days, one night). The cost per trip for two individuals is $2,500 which includes round trip coach airfare from San Diego to Washington, DC ($908); hotel room in Bethesda, MD ($150/night); University allowed per diem rate for meals ($46/day); taxi fare to and from both airports ($100). The team is expected to include Dr. Finer and one co-investigator or Ellen Milan, RNC depending on the meeting agenda. A 3% increment is included for subsequent years.

Other Expenses
A total of $2500 is requested: $900 for telephone, computer and fax line communication capabilities; $600 for postage and shipping of documents including express mail; $600 is included for printing of data forms and correspondence; and $400 is requested for publication expenses for abstracts and manuscripts arising from this project.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Neil N. Finer, M.D.	Professor Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Toronto, Toronto, Ontario	M.D.	1964-1968	Medicine
Wellesley Hospital, Toronto, Ontario		1967-1968	Rotating Internship
I.W.K. Children's Hospital, Halifax, Nova Scotia		1970-1971	Residency

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1973 - 1974	Fellow In Pediatric Pulmonary Disease and Neonatology	Children's Hospital Medical Centre, Harvard Medical School Boston Hospital for Women, Boston, MA
1974 - 1975	Senior Fellow - Neonatology	Joint Program in Neonatology, Harvard Medical School
1975	Assistant Professor	University of Alberta, Edmonton, Alberta
1975 – 1995	Director	Neonatal Intensive Care & Newborn Nurseries, Edmonton, Alberta
1976 – 1982	Associate Professor	University of Alberta, Edmonton, Alberta
1981 – 1995	Professor	University of Alberta, Edmonton, Alberta
1989 – 1994	Director	Extracorporeal Membrane Oxygenation Program, Edmonton, Alberta
1995 - Present	Director	Division Of Neonatology
	Professor	Department of Pediatrics University Of California, San Diego Medical Center

Articles (over 155 refereed publications; selection of 43 from 1991-2000)

1. Jamali F, Coutts RT, Malek F, Finer NN, Peliowski A. Lack of a interaction between doxapram and theophylline in apnea of prematurity. Dev Pharmacol Ther 1991;16:7882.
2. Finer NN, Muzyka D. Flexible endoscopic intubation of the neonate. Pediatr Pulmonol 12:48-51;1992.
3. Finer NN, Barrington KJ, Hayes BJ. Prolonged periodic breathing: Significance in sleep studies. Pediatr 89:450-453;1992.
4. Finer NN, Barrington KJ, Hayes BJ, Hugh A. Obstructive, mixed and central apnea in the neonate: Physiologic correlates. J Pediatr 121:943-950;1992.
5. Amitay M, Etches PC, Finer NN, Maidens MJ. Synchronous mechanical ventilation of the neonate with respiratory disease. Crit Care Med 21:118-124;1993.
6. Buckner PS, Maidens MJ, Finer NN. Characterization of the neonatal heart rate baroreflex during and after ECMO. Early Hum Dev 32:49-61;1993.
7. Finer NN, Woo BC, Hayashi A, Hayes BJ: Neonatal surgery: intensive care unit versus operating room. J Pediatr Surg 28:645-649;1993.
8. Robertson CMT, Finer NN. Long term follow-up of term neonates with perinatal asphyxia. In: Clinics in Perinatology. S Shankaran (ed). WB Saunders. Philadelphia. 1993, pp 483-500.
9. Barrington KJ, Finer NN. A randomized, controlled trial of aminophylline in ventilatory weaning of premature infants. Crit Care Med 21:846-850;1993.
10. Etches PC, Finer NN, Barrington KJ, Graham AJ, Chan WKY. Nitric oxide reverses acute hypoxic pulmonary hypertension in the newborn piglet. Pediatr Res 35:15-19;1994.
11. Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA. Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: Dose response. J Pediatr 124:302-308;1994.
11. Ryan CA, Perreault T, Johnston-Hodgson A, Finer NN. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia and cardiac malformations. J Pediatr Surg 1994;29:878-881.
12. Ryan CA, Finer NN. Changing attitudes and practices regarding local analgesia for newborn circumcision. Pediatrics 1994;94:230-233.
13. Tyebkhan J, Finer NN, Ryan CA. Elective cesarean section, iatrogenic prematurity and life threatening respiratory distress in infants referred for ECMO. J SOGC 1994;16:1909-1916.
14. Cheung PY, Finer NN. Plasma lactate concentration as a predictor of death in neonates with severe hypoxemia requiring extracorporeal membrane oxygenation. J Pediatr 1994;125:763-768.

15. Ryan CA, Finer NN, Barrington KJ. Effects of magnesium sulphate and nitric oxide in pulmonary hypertension induced by hypoxia in newborn piglets. Arch Dis Child 1994;71:F151-155.
16. Ryan CA, Finer NN. Antenatal corticosteroid therapy to prevent respiratory distress syndrome. J Pediatr 1995;126:317-319.
17. Peliowski A, Finer NN, Etches PC, Tierney AJ, Ryan CA. Inhaled nitric oxide for premature infants after prolonged rupture of the membranes. J Pediatr 1995;126:450-453.
18. McMillan D, Chernick V, Finer N, Schiff D, Bard H, Watts J, Krzeski R, Long W, and the Canadian Exosurf Neonatal Study Group. Effects of two rescue doses of synthetic surfactant in 344 infants with respiratory distress syndrome weighing 750 to 1249 grams: A double-blind, placebo-controlled multicenter Canadian trial. J Pediatr 1995;126:S90-S98.
19. Ryan CA, Finer NN, Etches PC, Tierney AJ, Peliowski A. Congenital diaphragmatic hernia: Associated malformations - cystic adenomatoid malformation, extralobular sequestration and laryngotracheoesophageal cleft: two case reports. J Pediatr Surg 1995;30:883-885.
20. Robertson CMT, Finer NN, Sauve RS, Whitfield MF, Belgaumkar TK, Synnes AR, Grace MGA. Neurodevelopmental outcome after neonatal extracorporeal membrane oxygenation. CMAJ 1995;152:1981-1988.
21. Barrington KJ, Finer NN, Peliowski A, Etches PC, Graham AJ, Chan WKY. Inhaled nitric oxide improves oxygenation in piglets with Meconium aspiration. Pediatr Pulmonol 1995;20:27-33.
22. Sigalet DL, Tierney AJ, Adolph V, Perreault T, Finer NN, Hallgren R, Laberge JM. Timing of repair of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation support. J Pediatr Surg 1995;30:1183-1187.
23. Barrington KJ, Finer NN, Chan W. A blind, randomized comparison of the circulatory effects of dopamine and epinephrine infusions in the normoxic newborn piglet during normoxia and hypoxia. Crit Care Med 1995;23:740-748.
24. Cheung PY, Robertson CMT, and Finer NN. Plasma lactate as a predictor of early childhood neurodevelopmental outcome of neonates with severe hypoxaemia requiring extracorporeal membrane oxygenation. Arch Dis in Childhood, Fetal and Neonatal Edn., 1996;74(1):F47-F50.
25. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. Pediatr Pulmonol 1996;21(1):48-51.
26. Young B, Shapira S, Finer NN. Predischarge car seat safety study for premature infants. Pediatr Child Health 1996;1:202-5.
27. Finer NN, Tierney AJ, Ainsworth W. Venovenous ECMO: The effects of proximal internal jugular cannulation. J Pediatr Surg 1996;31:1391-5.
28. Barrington K, Finer NN, Li D: Predischarge respiratory recordings in very low birthweight newborn infants. J Pediatr 1996;129:934-40.
29. Cheung PY, Barrington KJ, Pearson RJ, Bigam DL, Finer NN, Van Aerde JE: Systemic, pulmonary and mesenteric perfusion and oxygenation effects of dopamine and epinephrine. Am J Resp Crit Care Med 1997;155:32-7.
30. Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure: The Neonatal Inhaled Nitric Oxide Study Group (NINOS) (Co-Principal Investigator: Finer NN). A Collaboration of the Canadian Inhaled Nitric Oxide Study Group and the NICHD Neonatal Research Network. New Engl J Med 1997;336:597-604.
31. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatr 1997;99:838-45. (Co-Principal Investigator and Principal Author).
32. Steinhorn RH, Cox PN, Fineman JR, Finer NN, Rosenberg EM, Silver MM, Tyebkhan J, Zwass MS, Morin FC. Inhaled nitric oxide enhances oxygenation but not survival in infants with alveolar capillary dysplasia. J Pediatr 1997;130:417-22.
33. Cheung PY, Prasertsom W, Finer NN, Robertson CMT. Rescue high frequency oscillatory ventilation for preterm infants of birth weight 1250 grams and under: neurodevelopmental outcome and its prediction. Biol of the Neonate 1997;71:282-291.
34. Finer NN, Tierney AJ, Ainsworth W. Congenital diaphragmatic hernia: Developing a protocolized approach. J Pediatr Surg 1998;33:1331-37.
35. Cheung P-Y, Barrington KJ, Finer NN, Robertson CMT. Early childhood neurodevelopment in very low birth weight infants with predischarge apnea. Neonatal Intensive Care 1999;12:40-47.
36. Finer NN, Horbar JD, Carpenter, JH for the Vermont Oxford Network. Cardiopulmonary resuscitation in the very low birthweight infant: The Vermont Oxford Network Experience. Pediatr 1999;104:428-34.
37. Finer NN, Tarin T, Vaucher YE, Barrington K. Intact survival in extremely low birth weight infants after delivery room resuscitation. Pediatr 1999;104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e40.
38. Speziale M, Allen R, Henderson C, Barrington K, Finer NN. Effects of ibuprofen and indomethacin on the regional circulation in newborn piglets. Bio Neonate 1999;76(4):242-52.
39. Barrington KJ, Singh AJ, Etches PC, Finer NN. Partial liquid ventilation with and without inhaled nitric oxide in a newborn piglet model of meconium aspiration. Am J Respir Crit Care Med 1999;160:1922-27.
40. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide in term and near-term infants: Neurodevelopmental Follow-up. J Pediatr 2000;136:611-17. (Co-Principal Investigator and Principal Author)
41. Jacobs P, Finer NN, Robertson CMT, Etches P, Hall EM, Saunders LD. A cost effectiveness analysis of the application of nitric oxide versus oxygen gas for near-term newborns with respiratory failure: results from a Canadian randomized clinical trial. Crit Care Med 2000;28:872-78.

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Graham Bernstein, MD, FAAP	Director of Neonatal Respiratory Care

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of the Witwatersrand, Joannesburg, South Africa	MB.Bch.	1980	Bachelor of Medicine Bachelor of Surgery

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1987-1988	Clinical Instructor of Pediatrics	University of California, San Diego
1989-1996	Assistant Clinical Professor of Pediatrics	University of California, San Diego
1989-1992	Medical Director of Neonatal Services	Scripps Memorial Hospital of Chula Vista
1996-1999	Associate Clinical Professor of Pediatrics (Full-time faculty)	University of California, San Diego
1999-Present	Associate Clinical Professor of Pediatrics (Non-Salaried)	University of California, San Diego
2000-Present	Director of Neonatal Respiratory Care San Diego, CA	Sharp Mary Birch Women's Hospital NICU,

Publications

1. Waecker NJ, Davis CE, Bernstein G, and Spector, SA. Pleisiomonas shigelloides septicemia and meningitis in a newborn. Pediatr Infect Dis 1988;12:877-9.

2. Bernstein G, Heldt GP, and Mannino FL. Reliability and Response Time of a Real-Time Adjustable Ratio Patient Triggered Ventilation System in Neonates. Presented at the annual meeting of the Society for Pediatric Research, Washington DC, May 1989, Pediatr Res 1989;25:303A.

3. Bernstein G, Heldt GP, and Mannino FL. Reliability and Response Time of a Real-Time Variable Ratio Patient Triggered Ventilation System in Neonates. Presented at the annual meeting of the Western Society for Pediatric Research, Carmel CA, February 1989. Clin Res 1989;37:200A.

4. Bernstein G, Heldt GP, Mannino FL. More Consistent Tidal Volumes During Neonatal Synchronous Intermittent Mandatory Ventilation (SIMV) than IMV. Presented at the annual meeting of the Society for Pediatric Research, New Orleans LA, May 1991. Pediatr Res 1991;29:308A.

5. Bernstein G, Cleary JP, Rosas, JF, Schellenberg, LD, Mannino, FL, Heldt, GP. Response Time of Three Patient Triggered Infant Ventilators. Presented at the annual meeting of the American Society for Pediatric Research, Baltimore MD, May 1992. Pediatr Res 1992;31(4):195A.

6. Govindaswami B, Bejar R, Bernstein G, and Heldt GP. Cerebral Blood Flow Velocity (CBFV) Variability in Infants During Synchronized (SIMV) and Conventional Intermittent Mandatory Ventilation (IMV). Presented at the annual meeting of the Society for Pediatric Research, Baltimore MD, May 6, 1992. Pediatr Res 1992;31(4):203A.

7. Bernstein G, Cleary JP, Heldt GP, Rosas JF, Schellenberg LD, Mannino FL. The Response Time and Reliability of Three Neonatal Patient Triggered Ventilators. Am Rev Resp Dis 1993;148:358-364.

8. Bernstein G, Heldt GP, Mannino FL. Increased and More Consistent Tidal Volumes During Synchronized Intermittent Mandatory Ventilation in Newborn Infants. Am J Resp Crit Care Med 1994;150:1444-1448.

9. Heldt, GP and Bernstein G. "Patient Initiated Mechanical Ventilation." In: New Therapies for Neonatal Respiratory Failure: A Physiologic Approach." Eds: Boynton BR, Carlo WA, and Jobe AH. Cambridge Press, New York, 1994;Chapter 9:152-170.

10. Bernstein G, Heldt GP, Knodel E. Airway Leak Size in Neonates and Autocycling of Three Flow-Triggered Ventilators. Crit Care Med 1995;23:1739-44.

11. Cleary JP, Bernstein G, Mannino FL, Heldt GP. Improved oxygenation during synchronized intermittent mandatory ventilation in neonates with respiratory distress syndrome: a randomized crossover study. J Pediatr 1995;126(3):407-411.

12. Bernstein G, Mannino FL, Heldt GP, Callahan JD, Bull DH, Sola A, Ariagno RL, Hoffman GL, Frantz ID, Troche BI, Roberts JL, Dela Cruz TV, Costa E. Randomized Multicenter Trial Comparing Synchronized and Conventional Intermittent Mandatory Ventilation in Neonates. J Pediatr 1996;128:453-63.

13. Kiciman NM, Andreasson B, Bernstein G, Mannino FL, Rich W, Henderson C, Heldt GP. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. Pediatr Pulmonol 1998; 25:175-181.

14. Bernstein G. "InfantStar Ventilator." In: Manual of Neonatal Respiratory Care. Eds: Sinha SK and Donn S. Futura Publishing Co. Inc. New York, 2000; Chapter 32: 204-5.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Deirdre K. Browner, MPH	Data entry/statistician

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of California, Riverside	BS	1979	Biology (Honors)
San Diego State University	MPH	1990	Epidemiology & Biostatistics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1984 to 1986	Contract database coordinator	Naval Health Research Center, San Diego, CA
1987 to 1991	Staff Research Associate	University of California, San Diego, San Diego, CA
1985 to 1991	Programmer/Analyst	University of California, San Diego, San Diego, CA
1991 to 1995	Staff Research Associate	University of California, San Diego, San Diego, CA
1995 to 1998	Staff Research Associate	University of California, San Diego, San Diego, CA
1998 to 2000	Contract database coordinator	Self-employed
200 to present	Data entry/statistician	University of California, San Diego, San Diego, CA

PUBLICATIONS

1. Criqui MH, Browner D, Fronek A, Klauber MR, Barrett-Connor E, Coughlin SS, Gabriel S. Peripheral arterial disease in large vessels is epidemiologically distinct from small vessel disease: an analysis of risk factors. Am J Epidemiol 1989;129:1110-19.

2. Coughlin SS, Browner D, Criqui MH, Trock B. The logistic modeling of sensitivity and specificity of a diagnostic test. Presented at the annual meeting of Society for Epidemiologic Research, Birmingham, AL, June 14-16, 1989. Am J Epidemiol 1989;130:798.

3. Reaven PD, Barrett-Connor EL, Browner DK. Abnormal glucose tolerance and hypertension. Diab Care 1990;13(20):119-125.

4. Langer RD, Criqui MH, Fronek A, Browner D, Klauber MR. Isolated small vessel peripheral arterial disease is associated with fuiture cardiovascular events. Presented at the 30th Annual Conference on Cardiovascular Disease Epidemiology, March 29-31, 1990, San Diego, CA. Circulation 1990;81:724.

5. Ganiats TG, Browner DK. Measles immunization strategies. Fam Prac Res J 1991;11:429-32.

6. Coughlin SS, Trock B, Criqui MH, Pickle LW, Browner D, Tefft MC. The logistic modeling of sensitivity, specificity, and predictive value of a positive test. J Clin Epidemiol 1992;45:1-7.

7. Coughlin SS, Trock B, Criqui MH, Pickle LW, Browner D, Tefft MC. Dr. Diamond's "Clinical Epistemology of Sensitivity and Specificity." J Clin Epidemiol 1992;45:15-16.

8. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Peripheral arterial disease and subsequent all-cause, cardiovascular, and coronary heart disease mortality: A 10-year prospective study. N Engl J Med 1992;326:381-6.

9. Kashani IA, Kaplan RM, Rupp JW, Langer RD, McCann TJ, Sallis JF, Bracker M, Browner D, et al. Effects of a preventive cardiology curriculum on behavioral cardiovascular risk factors and knowledge of medical students. Pat Educ and Counsel 1993;21:15-27.

10. Palinkas LA, Browner D. Effects of prolonged isolation in extreme environments on stress, coping, and depression. J Appl Soc Psychol 1995;25:557-76.

11. Palinkas LA, Cravalho M, Browner D. Seasonal variation of depressive symptoms in Antarctica. Acta Psych Scand 1995;91:423-9.

12. Ganiats TG, Browner DK, Kaplan RM. Comparison of two methods of calculating quality-adjusted life years. Qual Life Res 1996;5:162-4.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Edmund V. Capparelli, Pharm.D.	Project Pharmacologist

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
San Diego State University, San Diego, California	___		Pre-Pharmacy
UC San Diego, La Jolla, California	___		Pre-Pharmacy
UC San Francisco, San Francisco, California	Pharm.D.	1985	Pharmacy

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Experience:

7/85 to 6/87	University of Connecticut, School of Pharmacy, Storrs, CT: Associate Clinical Professor in Clinical Pharmacy
7/85 to 6/87	Hartford Hospital, Hartford, CT: Clinical Pharmacy Fellow in Cardiovascular Therapeutics
7/87 to 7/88	University of California, Irvine Medical Center: Clinical Pharmacy Fellow with Division of Cardiology
7/88 to 12/89	University of California, Irvine Medical Center: Senior Pharmacist, Cardiology/Emergency Departments
12/98 to Present	University of California San Diego School of Medicine, Department of Pediatrics, Associate Clinical Professor,
1/94 to Present	University of California San Diego School of Medicine and Children's Hospital and Health Center's Pediatric Pharmacology Research Unit: Co - Director
1/93 to Present	AIDS Clinical Trials Group, National Institutes of Health: Member Pediatric Pharmacology Committee, Vice Chair (1/99 to present)
2/89 to Present	University of California, San Francisco School of Pharmacy: Assistant Clinical Professor
12/89 to Present	University of California, San Diego Medical Center: Pharmacokinetics Specialist, Clinical Pharmacokinetics Service

Publications:

1. Bakshi SS, Britto P, Capparelli EV, Mofeson L, Fowler MG, Rasheed S, Schoenfeld D, Zimmer B, Yogev R, Salgo M, Boone G, Pahwa SG. Evaluation of pharmacokinetics, safety, tolerance and activity of combination of zalcitabine and zidovudine (ZDV) in stable ZDV-treated, pediatric patients with HIV infection. J Infect Dis 175:1039-50 (1997).
2. Lemire J, Capparelli EV, Macdonald DJ, Griswold WR, Reznick V, Mendoza SA. Predictability and Reproducibility of Neoral Pharmacokinetics (PK) in Stable Pediatric Renal Transplant Recipients. Transplantation, December 64:12 (Abstract) (1997)
3. Taskintuna I, Rahhal FM, Capparelli EV, Cundy KC, Freeman WR. Intravitreal and plasma cidofovir concentrations after intravitreal and intravenous administration in AIDS patients with cytomegalovirus retinitis. J Ocular Pharmacol Therap 2:147-51 (1998).
4. Mirochnick M, Capparelli E, Dankner W, Sperling RS, Van Dyke R, Spector S. Zidovudine pharmacokinetics in premature infants exposed to HIV. Antimicrob Agent Chemother 42:808-812 (1998).
5. Dengler LD, Capparelli EV, Bastian JF, Bradley DJ, Glode MP, Santa S, Newburger JW, Baker AL, Mastsubara T, Burns JC. Cerebrospinal fluid profile in patients with acute Kawasaki Disease. Pediatr Infect Dis J 17:478-81 (1998).
6. Ting EC, Capparelli EV, Billman GF, Lavine JE, Matsubara T, Burns JC. Elevated gamma-glutamyltransferase concentrations in patients with acute Kawasaki disease. Pediatr Infect Dis J 17:431-2 (1998).

7. Capparelli EV, Connor J, Englund J, Baker C, Raskino C, Palumbo P, Spector. Population Pharmacokinetics (PK) and Pharmacodynamics (PD) of Didanosine (ddI) in Children with HIV Infection. 5th Conference on Retrroviruses and Opportunistic Infections. I21 (Abstract) (1998).
8. Capparelli EV, Connor JD, Englund E, Raskino C, Palumbo P, Baker C and PAGTG 152. Age Related Zidovudine Pharmacokinetic Differences in Infants and Children: An Association with Increased Toxicity? ICAAC (Abstract) (1998).
9. Capparelli E, Kovacs A, Husson R, Connor J, McLaren C and PAGTG 239. Pharmacokinetics of Didanosine in HIV Infected Infants. ICAAC (Abstract) (1998).
10. Capparelli, EV, Lemire JC, Benador N, Resnik V, Griswold WR, Connor JD. Population Pharmacokinetics of Cyclosporin A in Pediatric Renal Transplant Recipients. Pharmacotherapy 18:1166 (Abstract) (1998).
11. Capparelli EV, Romanowski GL, McFeely EJ, Murray W, Lane JR, Croutharmel P, Kildoo C, Connor JD. The Influences of Renal Function and Maturation on Vancomycin Elimination. Pharmacotherapy 18:1160 (Abstract) (1998).
12. Letendre SL, Capparelli EV, Ellis RJ, Durand D, McCutchan JA. Levels of Serum and Cerebrospinal Fluid (CSF) Indinavir (IND) and HIV RNA in HIV infected Individuals. Presented at 6th Conference on Retrroviruses and Opportunistic Infections 407 (Abstract) (1999).
13. Mirochnick M, Cooper E, Xu J, Lindsey J, Capparelli E, McIntosh K, McNamara J, Mofenson L. Population Pharmacokinetics of Dapsone in HIV-Infected Children. Pediatric Research 44:982A (Abstract)(1999).
14. Kim Y, Williams P, Lane J, Capparelli E, Liu J. Fluorocytosine: Population pharmacokinetic model development, nonparametric bootstrap validation dosing strategy evaluation. Presented at American Association of Pharamceutical Scientists (Abstract) (1999).
15. Mirochnick M, Cooper E, Xu J, Lindsey J, Capparelli E, McIntosh K, McNamara J, Mofenson L, Jacobus D. Population pharmacokinetics and pharmacodynamics of dapsone in HIV infected children. Presented at the 7th Conference on Retroviruses and Opportunistic infections 721 (Abstract) (2000).
16. Capparelli E, Burchett S, Kovacs A, Khoury M, Carey V, Smith E, Mofenson L, Connor J, Zimmer B, Hawkins E. Nelfinavir (NFV) pharmacokinetics in combination with ritonavir (RTV) in infants and children with advanced HIV disease. Presented at the 7th Conference on Retroviruses and Opportunistic infections 661 (Abstract) (2000).
17. Blascke AJ, Capparelli EV, Ellis RJ, Letendre SL, McCutchan JA. A population model based approach for determining lamuvidine (3TC) cerebrospinal fluid (CSF) penetration in HIV infected adults. Presented at the 7th Conference on Retroviruses and Opportunistic infections 310 (Abstract) (2000).
18. Mirochnick M, Capparelli EV, Connor JD. Pharmacokinetics of zidovudine in infants: a population analysis across studies. Clin Pharmacol Therap 66:16-24 (1999).
19. Mainwaring RD, Capparelli E, Schell K, Nelson JC. Pharmacokinetic evaluation of triiodothyronine supplementation following modified Fontan Procedure. Circulation 101:1423-1429 (2000).
20. Ellis RJ, Gamst AC, Capparelli E., Spector SA, Hsia K, Wolfson T, Abramson I, Grant I, McCutchan JA. HIV in cerebrospinal fluid derives in part form productive CNS infection. Neurology 54:927-936 (2000)
21. Bradley JS, Kearns GL, Reed MD, Capparelli EV, Vincent J. Pharmacokinetics of a new fluroquinolone, Trovafloxacin (CP 99,219) in infants and children following administration of a single intravenous dose of alatrofloxacin. Accepted for publication by Antimicrobial Agents Chemother (2000).
22. Capparelli E, Mirochnick M, Dankner W, Blanchard S, Mofenson L, Smith B, Cuipiak G, and Pediatric ACTG 331 Team. Population pharmacokinetics (PPK) of Zidovudine (ZDV) in premature HIV exposed neonates. Presented at Society for Pediatric Research (5/2000).
23. Sun H, Capparelli E, Lazor J, Connor J. Identifying Covariates in pediatric population pharmacokinetic (PPK) studies using method of partial resampling (PR) and bootstrapping (BT). Clin Pharmacol Therap 67:163 (abstract)(2000).
24. Letendre SL, Capparelli EV, Ellis RJ, McCutchan JA. Indinavir population pharmacokinetics in plasma and cerebrospinal fluid. Accepted for publication to Antimicrobial Agents Chemother (2000).
25. Frenkel LM, Capparelli EV, Dankner WM, Xu J, Smith IL, Ballow A, Culnane M, Read JS, Thompson M, Mohan KM, Shaver A, Robinson CA, Stempien MJ, Burchett SK, Melvin AJ, Borkowsky W, Petru A, Kovacs A, Yogev R, Goldsmith J, McFarland E, Spector SA. Oral ganciclovir in children: pharmacokinetics, safety, tolerance and antiviral effects. Accepted for publication J Infect Dis (2000).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Val Catanzarite, M.D., Ph.D.	Director, Perinatal Imaging, Sharp Perinatal Center

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
California Institute of Technology, Pasadena, CA	B.S.	1971-74	Math/Biology
University of California, San Diego, San Diego, CA	M.D.	1974-80	Medicine
University of California, Berkeley, Berkeley, CA	Ph.D.	1977-80	Biophysics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Current Positions:

Director, Perinatal Imaging, Sharp Perinatal Center
Co-Director, Sharp/Children's Prenatal Diagnostic Center
Assistant Clinical Professor, Department of Reproductive Medicine,
University of California, San Diego, School of Medicine (Voluntary)

Prior Positions:

1989-90 Director, The Perinatal Center, San Diego, CA
1988-89 Assistant Professor of Obstetrics and Gynecology
Perinatal Consultant, Arkansas Perinatal Outreach Education Program
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of Arkansas for Medical Sciences
1986-87 Assistant Professor of Obstetrics and Gynecology
Director, Obstetrics Special Care Unit
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of New Mexico Medical Center

SELECTED PUBLICATIONS:

1. Mekouris RW, Miller FC, Catanzarite VA, et al: Increase in the plasma levels of the N-terminal and C-terminal portions of the prohormone of atrial natriuretic factor during normal pregnancy. Am J Obstet Gynecol, 1990;162:859-64.
2. Brandt-Graham S, Catanzarite VA, Bernstein J, Varela-Gittings F: A Comparison of Attitudes and Practices of Episiotomy Among Obstetrical Practitioners in New Mexico. Soc Sci Med, 1990;31:191-201.
3. Catanzarite VA, Quirk JG: Papular Dermatoses of Pregnancy. Clin Obstet Gynecol, 1990;33:754-758.
4. Jelovsek FR, Catanzarite VA, Price RD, Stull RE: Learning Theory and Knowledge Structures in Computer-Aided Instruction. MD Computing, 1990;7:98-103.
5. Catanzarite VA, Quirk JG: Determinants of Visualization of Fetal Anatomy at Second Trimester Sonography. Am J Obstet Gynecol, 1990;163:191-5.
6. Merkouris RW, Miller FC, Catanzarite VA, et al: The N-terminal and C-terminal Portions of the Atrial Natriuretic Factor Prohormone Increase During Preeclampsia. Am J Obstet Gynecol, 1991;164:1197-202.
7. Catanzarite VA, Mendoza A, Chapman T, Muller W and Maida CS: Early Prenatal Diagnosis of Type II Cystic Adenomatoid Malformation of the Lung: Sonographic and histological findings. J Ultrasound Obstet Gynecol, 1992;2:129-132.
8. Catanzarite VA, Foster E, Robinette P, Cousins LM, Schneider JM: Maternal Death Due to Rupture of a Low Transverse Cesarean Section Incision During Labor at Home. Western J Med, 1992;157:454-455.
9. Aisenbrey GA, Corwin E, Catanzarite VA. Effect of magnesium sulfate on the vascular actions of norepinephrine and angiotensin II. Am J Perinat 1992;9(5-6):477-80.
10. Catanzarite VA, Danker W: Prenatal Diagnosis of Congenital Cytomegalovirus Infection: False-negative amniocentesis at 20 weeks' gestation. Prenatal Diagnosis, 1993;13:1021-25.

11. Catanzarite VA, Wozniak P, Maida CS, Mascarello JT, Senac MO: Meconium Peritonitis. THE FETUS, 1993;3:4-7.
12. Weyerts LK, Catanzarite VA, Jones MC, Mendoza A: Prenatal Diagnosis of a Giant Intracranial Teratoma Associated with Pulmonary Hypoplasia. J Med Genetics, 1993;30:880-2.
13. Mascarello JT, Jones MC, Catanzarite VA, Brown KH: Mosaic Triple Trisomy in a Phenotypically Normal Fetus. Prenatal Diagnosis, 1994;14:163-65.
14. Catanzarite VA, Schibanoff JM, Chinn R, Mendoza A, Weiss R: Overwhelming Maternal Sepsis Due to a Gas-forming E. Coli Chorioamnionitis. Am J Perinatol, 1994;11(3):205-207.
15. Catanzarite VA, Mehalek KE, Maida CS, Mendoza A: Early Sonographic Diagnosis of Intrapericardial Teratoma. Ultrasound Obstet Gynecol, 1994;4(6):505-507.
16. Hurley TJ, Montgomery R, Waldron JA Jr., Catanzarite VA, Quirk JG: Fatal Course of Malignant Non-Hodgkin's Lymphoma of T-cell Type During Pregnancy with Metastasis to the Fetus. J Maternal-Fetal Med, 1994;3:69-74.
17. Catanzarite VA, Thomas SJ, Dixson B. Confronting Fetal Demise. Contemporary Obstetrics and Gynecology, 1994;39(11):29-42.
18. Catanzarite VA, Hendricks SK, Maida CS, Westbrook C, Cousins LM, Schrimmer DB: Prenatal Diagnosis of the Two Vessel Cord: Implications for management of pregnancy. Ultrasound in Obstet Gynecol, 1995;15:98-105.
19. Catanzarite VA, Schrimmer DB, Maida CS. Antenatal Sonographic Diagnosis of Intracranial Hemorrhage in Association with Sinusoidal Fetal Heart Rate Tracing. Prenatal Diagnosis, 1995;15(3):229-235.
20. Catanzarite VA, Deutchman M, Johnson CA, Scherger JE. Pregnancy after 35: What's the real risk? Patient Care. January 1995, 41-51.
21. Catanzarite, VA, Stein DA: Crystal and Pregnancy: Methamphetamine associated maternal mortality. Western J Med 1995;162:454-457.
22. Catanzarite VA, Steinberg S, Moseley C, Landers C, Cousins LM, Schneider JM: Severe Preeclampsia with Fulminant and Extreme Elevation of aspartate aminotransferase and lactate dehydrogenase levels: High risk for maternal death. Am J Perinatol, 1995;12(5):310-313.
23. Aisenbrey GA, Catanzarite VA, Hurley TJ, Spiegel JH, Schrimmer DB, Mendoza A. Monoamniotic and pseudomonoamniotic twins: Sonographic diagnosis, detection of cord entanglement, and obstetric management, Obstet Gynecol 1995;86:218-22.
24. The Collaborative Home Uterine Monitoring Study (CHUMS) Group. A multicenter randomized controlled trial of home uterine monitoring: Active vs. sham device. Am J Obstet Gynecol 1995;173:1120-7.
25. Catanzarite VA, Mehalek KE, Wachtel T, Westbrook C. Sonographic diagnosis of traumatic and later recurrent uterine rupture. Am J Perinatol 1996;13(3):177-180.
26. Pretorius DH, Chau C, Poeltler DM, Mendoza A, Catanzarite VA, Hollenbach KA. Placental cord insertion Visualization with prenatal ultrasonography. J Ultrasound Med 1996;15:585-593.
27. Catanzarite VA, Willms DC, Holdy KE, Gardner SE, Ludwig DM, Cousins LM. Brain death during pregnancy: Tocolytic therapy and aggressive maternal support on behalf of the fetus. Am J Perinatol 1997;14:429-32.
28. Catanzarite VA, Novotny WF, Cousins LM, Schneider JM. Pregnancies in a patient with congenital absence of prothrombin activity: Case report. Am J Perinatol 1997;14:135-138.
29. Pending Publication
30. Catanzarite VA, Low RN, Wong DY. Ovarian vein thrombosis during cesarean section: A report of two cases. J Reprod Med 1997;42:315-318.
31. Pending Publication
32. Pending Publication
33. Pretorius DH, Halsted MJ, Abels W, Catanzarite VA, Kaplan G. Hydroceles identified prenatally: A common physiologic phenomenon? J Ultrasound Med 1998;17:49-52.
34. Aisenbrey GA, Catanzarite VA, Nelson C. External cephalic version: Predictors of success. Obstet Gynecol 1999;94:783-6.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Gregory P. Heldt, M.D.	Professor of Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Stanford University, Palo Alto, CA	B.S.	1969	Chemistry
Catholic University of Leuven, Belgium		1969-70	Protein chemistry
University of California, San Diego, San Diego, CA	M.D.	1970-1974	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1974-1975	Research Fellowship in Neonatology	University of California, San Diego
1975-1976	Pediatric Internship	University of California, San Francisco
1976-1977	Pediatric Research	University of California, San Francisco
1977-1980	Fellowship in Neonatal-Perinatal and Pulmonary Medicine	University of California, San Francisco and Cardiovascular Research Institute, San Francisco
1985-present	Attending Neonatologist	University of California, San Diego Medical Center
1986-1988	Assistant Professor of Pediatrics	University of California, San Diego Medical Center
1988-1994	Associate Professor of Pediatrics	University of California, San Diego Medical Center
1994-present	Professor of Pediatrics	University of California, San Diego Medical Center

SELECTED PUBLICATIONS (1990-2000)

1. Pesonen E, Merritt TA, Heldt GP, Sahn DJ, Elias W, Tikkanen I, Fyhrquist R, Anderson S. Correlation of patent ductus arteriosus shunting with plasma natriuretic factor concentration in preterm infants with respiratory distress syndrome. Pediatr Res 1990;27:137-139.
2. Nielson DW, Heldt GP, Tooley WH. Stridor and gastroesophageal reflux in infants. Pediatr 1990;85(6):1034-1039.
3. Heldt GP. Member of the HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: assessment of pulmonary function at 9 months of corrected age. J Pediatr 1990;116(6):933-941.
4. Heldt GP. Member of the HIFI Study Group. High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. J Pediatr 1990;117(6):939-46.
5. Merritt TA, Hallman M, Berry C, Pohjavouri M, Edwards DK, Jaaskelainen J, Graff M, Vaucher Y, Wozniak P, Heldt GP, Rapola J. Randomized, placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. J Pediatr 1991;118(4):581-594.
6. Gillard N, Pappert D, Merritt TA, Heldt GP, Spragg RG. Radiolabelling of the hydrophobic components of lung surfactant with 3-(trifluoromethyl)-3-m[^{125}I]iodophenyl)diazirine. Analy Biochem 1991;193:1-6.
7. Heldt GP. Monitoring lung volumes in infants during and after intensive care. Presented at the Second Annual International Congress of Neonatology and Pediatrics, Courmayeur, Italy. Develop Physiopath Clin 1991;2(3):189-198.

8. Revak SD, Merritt TA, Hallman M, Heldt GP, La Polla RJ, Hoey K, Houghten RA, Cochrane CG. The use of synthetic peptides in the formation of biophysically active pulmonary surfactants. Pediatr Res 1991;29(5):460-465.
9. Heldt GP, Mohn MT, McWilliams R, Rosas F, Price D. Performance of an automated multiple-breath occlusion techniques for measurement of respiratory system compliance. Proceedings of the 4th International Conference on Fetal and Neonatal Physiological Measurements, Elsevier Press, The Netherlands, 1991.
10. Liu A, Hahn JS, Heldt GP, Coen RW. Detection of neonatal seizures through computerized EEG analysis. *Electroencephalo Clin Neurophysi* 1992;82(1):30-7.
11. Heldt GP, Merritt TA, Golembeski D, Gilliard N, Bloor C, Spragg R. Distribution of surfactant, lung compliance, and aeration of preterm rabbit lungs after surfactant therapy and conventional and high-frequency oscillatory ventilation. Pediatr Res 1992;31(3):270-5.
12. Olson TS, Woodson GE, Heldt GP. Upper airways function in Ondine's curse. Arch Otolaryng - Head and Neck Surgery 1992;118(3):310-2.
13. Vaucher YE, Harker L, Merritt TA, Hallman ML, Gist K, Bejar R, Heldt GP, Edwards D, Pohjavuori M. Outcome at twelve months of adjusted age in very low birth weight infants with lung immaturity: a randomized placebo-controlled trial of human surfactant. J Pediatr 1993;122(1):126-132.
14. Pesonen E, Heldt GP, Merritt TA, Sahn DJ, Elias W, Tikkanen I, Fyhrquist F, Andersson S. Atrial natriuretic factor and pulmonary status in premature infants with respiratory distress syndrome: preliminary investigation. Pediatr Pulmon 1993;15(6):362-4.
15. Bernstein G, Cleary JP, Heldt GP, Rosas JF, Schellenberg, LD, and Mannino FL. Response time and reliability of three neonatal patient-triggered ventilators. Am Rev Resp Dis 1993;148:358-364.
16. Bernstein G, Heldt GP, Mannino FL. Synchronous mechanical ventilation of neonates. Crit Care Med 1993;21:1984-85.
17. Gilliard N, Heldt GP, Loredo J, et al. Exposure of the hydrophobic components of porcine lung surfactant to oxidant stress alters surface tension properties. J Clin Invest 1994;93:2608-15.
18. Bernstein G, Knodel E, Heldt GP. Airway leak size in neonates and autocycling of three flow-triggered ventilators. Crit Care Med 1995;23:1739-44.
19. Cleary JP, Bernstein G, Mannino FL, Heldt GP. Improved oxygenation during synchronized intermittent mandatory ventilation in neonates with respiratory distress syndrome: A randomized, crossover study. J Pediatr 1995;126:407-11.
20. Merritt TA, Heldt GP. Partial liquid ventilation—the future is now. New Engl J Med 1996;335:814-5.
21. Cochrane CG, Revak SD, Merritt TA, Heldt GP, et al. The efficacy and safety of KL4-surfactant in preterm infants with respiratory distress syndrome. Am J Resp Crit Care Med 1996;153:404-10.
22. Revak SD, Merritt TA, Cochrane CG, Heldt GP, et al. Efficacy of synthetic peptide-containing surfactant in the treatment of respiratory distress syndrome in preterm infant Rhesus monkeys. Pediatr Res 1996;39:715-24.
23. Pappert D, Gillliard N, Heldt G, et al. Effect of N-nitroso-N-methylurethane on gas exchange, lung compliance, and surfactant function of rabbits. Inten Care Med 1996;22:345-52.
24. Bernstein G, Mannino FL, Heldt GP, et al. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr 1996;128:453-63.
25. Liu EA, Heldt GP. A trial of the safety of inhaled beclomethasone in ventilator-treated neonates. J Pediatr 1996;129:154-6.
26. Bernstein G, Heldt GP, Mannino FL. Body surface and airway triggered ventilation in extremely premature infants [letter]. Acta Pediatr 1997;86:1275-6.
27. Kiciman NM, Andréasson B, Bernstein G, Mannino FL, Rich W, Henderson C, Heldt GP. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. Pediatr Pulmonol 1998;25:175-81.

BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Frank Mannino, M.D.	Professor of Clinical Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Knox College, Galesburg, Illinois	B.A.	1968	Chemistry
Washington University School of Medicine, St. Louis, Missouri	M.D.	1972	Medicine
St. James Children's Hospital, Lt. Louis, Missouri	Intern/Resident	172-76	Pediatrics
UCSD Medical Center, San Diego, California	Fellow	1974-76	Neonatal/Perinatal Medicine
UCSD Medical Center, San Diego, California	Research Fellow	1976-77	Neonatal/Perinatal Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1976 Assistant Professor of Pediatrics, University of California, San Diego
1985 - 1994 Associate Adjunct Professor of Pediatrics, University of California, San Diego
1994 present Professor of Clinical Pediatrics, University of California, San Diego

Government and Community Service:

1985 – present Chair (1997), California Children's Services (CCS), Neonatology Technical Advisory Committee
1997 – present March of Dimes, San Diego/Imperial County Health Professional Advisory Committee

Selected Publications

1. Randel RC, Mannino FL. One-Lung High-Frequency Ventilation in the Management of an Acquired Neonatal Pulmonary Cyst. J Perinatol 1989;9(1):66-68.
2. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants: Assessment of pulmonary function at 9 months of corrected age. J Pediatr 1990;116(6):933-941.
3. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: Neurodevelopmental status at 16 to 24 months of postterm age. J Pediatr 1990;117:939-46.
4. Liu E, Benirschke K, Scioscia A, Mannino FL. Intrauterine death in multiple gestation. Acta Geneticae Med Gemellog 1992;41:5-26.
5. Bernstein G, Cleary JP, Heldt GP, Rosas JF, Schellenberg LD, Mannino FL. Response time and reliability of three neonatal patient-triggered ventilators. Am Rev Resp Dis 1993;148:358-364.
6. Liu EA, Mannino FL, Lane TA. Prospective, randomized trial of the safety and efficacy of a limited donor exposure transfusion program for premature neonates. J Pediatr 1994;123(1):92-6.
7. Bernstein G, Heldt GP, Mannino FL. Increased and more consistent tidal volumes during synchronized intermittent mandatory ventilation in newborn infants. Am J Resp Crit Care Med 1994;*150(pt 1):1444-8.*
8. Cleary, JP, Bernstein G, Mannino FL, Heldt GP. Improved oxygenation during synchronized intermittent mandatory ventilation in neonates with respiratory distress syndrome: a randomized, crossover study. J Pediatr 1995;126(3):407-11.
9. Baergen RN, Boue DR, Mannino F. Placental pathology casebook. Liveborn twin of an extramembranous pregnancy. J Perinatol 1995;15(6):510-3.

10. Wang-Rodriguez J, Mannino FL, Liu E, Lane TA. A novel strategy to limit blood donor exposure and blood waste in multiply transfused premature infants. Transfus 1996;36(1):64-70.
11. Bernstein G, Mannino FL, Heldt GP, Callahan JD. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr 1996;128(4):453-63.
12. Chang DG, Stein MT, Sine DA, Yeung DW, Mannino FL. Reversible Neonatal Cholestasis Following In Utero Exposure to Valproic Acid. McGill J Med 1996;2(2):89-92.
13 Mannino FL and Heldt G. Infant Respiratory Distress Syndrome. Chapter 70:p. 333-38. In: Manual of Clinical Problems in Pulmonary Medicine, 4th ed. Editors: Bordon RA and Moser KM. Little, Brown and Co., Boston, 1996.
14. Trauner DA and Mannino FL. Brain reorganisation after injury in infancy (letter). Lancet 1996;347:1701.
15. Bernstein G, Heldt GP, Mannino FL. Body surface and airway triggered ventilation in extremely premature infants. Acta Paediatr 1997;86(11):1275-6.
16. Adams-Chapman IS, Vaucher YE, Bejar RF, Benirschke K, Baergen R, Mannino FL. Association of maternal floor infarction of the placenta and neonatal white matter injury. Pediatr Res 1997;41:190A.
17. Ho BT, Vaucher YE, Moore TR, Mannino FL. Readmission risks of infants discharged early: case/control Study. Pediatri Res 1997;41:198A.
18. Vaucher YE, Campbell D, Ho BT, Mannino FL. Neonatal readmission: Importance of inadequate enteric intake. Pediatr Res 1997;41:212A.
19. Ballard RA, Ballard PL, Boardman C, Cnaan A, Davis DJ, Hart MC, Mannino FL, et al. Antenal thyrotropin releasing hormone (TRH) for the prevention of chronic lung disease (CLD) in the preterm infant. Pediatr Res 1997;41:246A.
20. Goldstein M, Kopotic R, Rich W, Liberman R, Vogt J, Ernesto G, Stephenson C, Mannino F. Acoustic correlatives of chest wall volumetric motion during high frequency oscillation (HFO). Pediatr Res 1997;41:253A.
21. Ballard RA, Ballard PL, Cnaan A, Pinto-Martin J, Davis DJ, Padbury JF, Phibbs RH, Parer JT, Hart MC, Mannino FL, Sawai SK. Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. North American Thyrotropin-Releasing Hormone Study Group. New Engl J Med 1998;19;338(8):493-8.
22. Gambling DR, Reisner LS, Mannino FL. Epidural analgesia and neonatal fever. Pediatr 1998;101(3 Pt 1):491-2; discussion 493-4.
23. Kiciman NM, Andreasson B, Bernstein G, Mannino FL, Rich W, Henderson C, Heldt GP. Thoraco-abdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. Pediatr Pulmonol 1998;43(5):660-5.
24. Speziale MV, Mannino FL, Hastings RH, Deftos LJ. Parathyroid hormone-related protein in tracheal aspirates of newborn infants. Pediatr Res 1998 May;43(5):245-9.
25. Ballard PL, Ballard RA, Ning Y, Cnann A, Boardman C, Pinto-Martin J, Polk D, Phibbs RH, Davis DJ, Mannino FL, Hart M. Plasma thyroid hormones in premature infants: effect of gestational age and antenatal thyrotropin-releasing hormone treatment. TRH Collaborative Trial Participants. Pediatr Res 1998;44(5):642-9.
26. Wang-Rodriguez J, Fry E, Fiebig E, Lee T, Busch M, Mannino FL, Lane TA. Immune response to blood transfusion in very-low-birthweight infants. Transfus 2000;40(1):25-34.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
Ellen-Marie Milan RNC	Neonatal Clinical Research Nurse

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Beth Israel Medical Center School of Nursing	RN	1969-72	Nuring

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Experience

06/72 to 09/75	Staff Nurse, Riverview Hospital, Newborn Nursery, Red Bank, New Jersey
09/75 to 06/78	Staff Nurse and Charge Nurse (5/76 to 9/77), Monmouth Medical Center, Regional Newborn Center, Long Branch, New Jersey
08/78 to 11/79	Clinical Nurse I→II, UCSD Medical Center, Infant Special Care Center
11/79 to 02/81	Administrative Nurse I-II (nights), UCSD Medical Center, Infant Special Care Center
02/81 to 05/82	Clinical Nurse III, UCSD Medical Center, Infant Special Care Center
05/81 to 10/82	Clinical Nurse IV, Neonatal Nurse Educator (temporary position), UCSD Medical Center, Infant Special Care Center
03/86 to 03/89	Research Nurse, High-Frequency Oscillatory Ventilation Compared with Conventional Mechanical Ventilation in the Treatment of Respiratory Failure in Preterm Infants, UCSD Medical Center
01/95 to 05/97	Research Nurse, TRH and the Prevention of Chronic Lung Disease Trial, UCSD Medical Center, San Diego Naval Medical Center and Kaiser Foundation Hospital San Diego
09/96 to 12/97	Research Nurse, Safety and Efficacy of Filgrastim in the Treatment of Late-Onset Neonatal Sepsis, UCSD Medical Center
10/82 to present	Clinical Nurse III, UCSD Medical Center, Infant Special Care Center

Teaching Experience

11/95	New Issues in Neonatal Nursing. Southern California Association of Neonatal Nurses Annual Conference. Presentation: *Steriods, Thyrotropin-Releasing Hormone, Erythropoietin and more...*
11/96	Project Concern International Romanian NEWSTART Program. Bucharest, Rimnicu Vilcea, Alba Iulia and Botosani, Romania. Presentations: *Modes of assisted ventilation of the neonate; Complications and hazards of assisted ventilation of the neonate; Care and monitoring of the infant receiving assisted ventilation.* Workshops: *Intubation of the neonate; Case scenarios of infants requiring assisted ventilation; Physical assessment of the neonate for nurses (including the use of a stethoscope)*
10/97	Changing Tides in Neonatal Care. Southern California Association of Neonatal Nurses Annual Conference. Presentation: *Granulocyte colony-stimulation factor: a new therapy in the NICU?*
09/99	March of Dimes, San Diego-Imperial Counties Board Meeting. Presentation: *Neonatal Intensive Care Today*
10/99	International Relief Teams' Neonatal Training Program Clinical Module. Riga, Lativia.

02/00 Project Concern International Romanian NEWSTART Program. Bucharest and Sighisoara, Romania. Preparation for Clinical Training Module in October 2000

Research Experience

09/96 to 12/97 Research Nurse, Safety and Efficacy of Filgrastim in the Treatment of Late-Onset Neonatal Sepsis. UCSD Medical Center.
Responsibilities: Monitor adherence to research protocol. Conduct inservices regarding research protocol. Perform data collection per the guidelines of AMGEN. Respond to research needs at all hours. Assure parent understanding of the nature of the research. Maintain records of infants enrolled. Prepare for site visits.

01/95 to 05/97 Research Nurse, TRH and the Prevention of Chronic Lung Disease Trial. UCSD Medical Center, San Diego Naval Medical Center and Kaiser Foundation Hospital San Diego.
Responsibilities: Monitor adherence to research protocol. Conduct inservices regarding research protocol. Perform data collection per the guidelines of The Children's Hospital of Philadelphia. Produce monthly reports. Coordinate collection of blood samples from enrolled infants at UCSD Medical Center; process blood samples. Respond to research needs at all hours. Assure parent understanding of the nature of the research. Maintain records of mothers and infants enrolled. Prepare for site visits.

03/86 to 03/89 Research Nurse, High-Frequency Oscillatory Ventilation Compared with Conventional Mechanical Ventilation in the Treatment of Respiratory Failure in Preterm Infants. UCSD Medical Center.
Responsibilities: Monitor adherence to research protocol. Conduct inservices regarding research protocol. Randomize eligible patients. Perform data collection per the guidelines of National Institutes of Health and the Research Triangle Institute. Respond to research needs at all hours. Assure parent understanding of the nature of the research. Maintain records of infants enrolled. Assist with neurodevelopmental follow-up and pulmonary function testing.

Publications

Ballard RA, Ballard PL, Cnaan A, Pinto-Martin J, Davis DJ, Padbury JF, Phibbs RH, Parer JT, Hart MC, Mannino FL, Sawai SK, et al. Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. North American Thyrotropin-Releasing Hormone Study Group. N Engl J Med, 1998 February 19;338(8):493-8.

Ellen-Marie Milan and Edward J McFeeley, *Memory Bank for Neonatal Drugs,* Williams and Wilkins, Baltimore, June 1990.

SCANN News, the newsletter of the Southern California Association of Neonatal Nurses Editor (11/94 to 12/98) and contributor.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
THOMAS R. MOORE	**Professor and Chairman of Reproductive Medicine**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	B.A.	1969	American Studies
Yale University, New Haven, CT	M.D.	1979	Medicine
Naval Hospital, San Diego, CA	Residency	1983	Obstetrics-Gynecology
UCSD School of Medicine, San Diego, CA	Fellowship	1985	Maternal-Fetal Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Experience:

1985-1988 Director of Perinatal Medicine and Obstetrics, Naval Hospital, San Diego, CA
1988-present Director, Division of Perinatal Medicine, UCSD Medical Center, San Diego, CA
1996-present Chairman, Department of Reproductive Medicine, UCSD Medical Center, San Diego, CA

Honors and Awards:

Honors for M.D. Thesis, Yale University, 1979
Connecticut Society of Obstetrics and Gynecology Outstanding Student Award, 1979
Resident Paper Award, Armed Forces District Meeting, 1983
Joseph M. Didio Memorial Teaching Award, University of California, San Diego, 1985
Ob-Gyn Resident Teaching Award, Naval Hospital, San Diego, 1986
Navy Commendation Medal for reducing perinatal morbidity and mortality, Naval Hospital, San Diego, 1985-1986
Intern Class Commendation for Outstanding Teaching, Naval Hospital, San Diego, 1987
Ob-Gyn Resident Teaching Award, Naval Hospital, San Diego, 1987
Searle-Richardson Prize for Best Junior Fellow Paper presented at an ACOG District Meeting-1987
Thomas R. Moore Award for Best Resident in Obstetrics inaugurated, Naval Hospital, San Diego, 1988
Humana Award for Excellence in Clinical Research, Society of Perinatal Obstetricians, 1991
Kaiser Permanente Award for Excellence in Teaching, Honorable Mention, 1991
Joseph M. Didio Memorial Teaching Award, University of California, San Diego, 1992
APGO Excellence in Teaching Award, University of California, San Diego, 1995

Publications:

Reiter RC, Jones GR, **Moore TR**. Paternal race, team birth weight, and risk for dystocia among Malaysian gravidas. Am J Gynecol Health 1991;V(4):25-29.

Brace RA, **Moore TR.** Diurnal rhythms in fetal urine flow, vascular pressures and heart rate in the sheep. J Am Physiol Soc 1991;261:1015-22.

Gilbert WM, **Moore TR**, Resnik R, Doemeny J, Chin H, Bookstein. Angiographic embolization in the management of hemorrhagic complications of pregnancy. Am J Obstet Gynecol. 1992;166:493-7.

Walker MPR, **Moore TR**, Brace RA. Urinary and cardiovascular responses to indomethacin infusion in the ovine fetus. Am J Obstet Gynecol. 1992;167:834-43.

Walker MPR, **Moore TR**, Cheung CY, Brace RA. Indomethiacin-induced urinary flowrate reduction in the ovine fetus is associated with reduced free water clearance and elevated plasma AVP levels. AM J Obstet Gynecol. 1992;167:1723-31.

Dankner WE, Dixon SD, Lane TA, **Moore TR**. Hepatitis B in a perinatal population. Letter. JAMA 1992; 269:589.

Kelly TF, **Moore TR**, Brace RA. Hemodynamic and fluid responses to furosemide infusion in the ovine fetus. Am

J Obstet Gynecol. 1993; 168:260-8.
Shields LE, Gan EA, Murphy HF, Sahn DJ, **Moore TR**. The prognostic value of hemoglobin A1c (HbA1c) in predicting fetal heart disease in diabetic pregnancy. Obstet Gynecol. 1993; 81:954-7.
Hedriana H, **Moore TR**. Ultrasonographic evaluation of human fetal urinary flow rate: accuracy limits of bladder-volume estimation. Am J Obstet Gynecol. 1994:170:1250-4.
Walker MPR, **Moore TR**, Brace RA. Indomethiacin and arginine vasopressin in the fetal kidney: a mechanism of oliguria. Am J Obstet Gynecol. 1994;171:1234-41.
Moore TR, Iams JD, Creasy RK, Burau KD, Davidson AL. Diurnal and gestational patterns of uterine activity in normal human pregnancy. Obstet Gyencol. 1994;83:517-523.
Hedriana HL, **Moore TR**. Comparison of single vs multiple growth sonography in predicting birth weight. Am J Obstet Gynecol 1994; 170: 1660-6.
Hedriana HL, **Moore TR**. Accuracy limits of ultrasonographic estimations of human fetal urinary flow rate. Am J Obstet Gynecol. 1994; 171:989-92.
Messersmith-Heroman K, Heroman WM, **Moore TR**. Pregnancy outcome in military and civilian women. Military Med 1994; 159:577-579.
Greenberg LR, **Moore TR**, Murphy H. Gestational Diabetes Mellitus: antenatal variables as predictors of Postpartum glucose intolerance. Obstet Gynecol 86:97, 1995.
Gilbert WM, Hanson LX, Mosquera M, **Moore TR**. The cost effectiveness of rubella screening in an indigent Population. J Mat Fet Med 4:262, 1995.
Moore TR. Assessments of amniotic fluid volume in at-risk pregnancies. Clin Obstet Gynecol 38:778, 1995.
Moore TR. Patterns of human uterine contractions: implications of clinical practice. Sem Perinatol 19:64, 1995.
Zaid A, Fullerton JT, **Moore TR**. Factors affecting access to prenatal care for U.S./Mexico border-dwelling Hispanic women. J Nurse-Midwifery 41:277, 1996.
Moore TR. Oligohydramnios. In Protocols for High Risk Pregnancy, 3rd Edition. Queenan JT, Hobbins JC, Eds. Blackwell Science, Cambridge, MA, 1996.
Tipton EE, **Moore TR**. Amniotic Fluid Regulation and Non-immune Hydrops. In Neonatal-Perinatal Medicine, 6th Edition. Fanaroff AA, Martin RJ, eds. C.V. Mosby, New York, 1997.
Gruslin-Giroux A, **Moore TR**. Erythroblastosis Fetalis, In Neonatal-Perinatal Medicine, 6th Edition. FanaroffAA, Martin RJ, eds. C.V. Mosby, New York,1997.
Moore TR. Clinical assessment of amniotic fluid. Clin Obstet Gynecol 40(2):303, 1997.
Moore TR. Fetal growth in diabetic pregnancy. Clin Obstet Gynecol 40:771, 1997.
Payne SD, Resnik R. **Moore TR**, Hedriana HL, Kelly TF. Maternal characteristics and risk of severe neonatal thrombocytopenia. Am J Obstet Gynecol 177(1): 149, 1997.
Moore TR. Diabetes in Pregnancy. In Shaffer and Avery's Diseases of the Newborn, 7th Edition. Taeusch HW, Ballard RA, Avery ME, eds. W.B. Saunders, Philadelphia, 1998.
Kelly TF, **Moore TR**. Maternal Medical Complications of Pregnancy. In Shaffer and Avery's Diseases of the Newborn, 7th Edition. Taeusch HW, Ballard RA, Avery ME, eds. W.B. Saunders, Philadelphia, 1998.
Roberts DL, **MooreTR**. Intrapartum Management. In Shaffer and Avery's Diseased of the Newborn 7th Edition. Taeusch HW, Ballard RA, Avery ME, eds. W.B. Saunders, Philadelphia, 1998.
Hull A, **Moore TR**. Antepartum Fetal Assessment. In Shaffer and Avery's Diseases of the Newborn, 7th Edition. Taeusch HW, Ballard RA, Avery ME, eds. W.B. Saunders, Philadelphia, 1998.
Sohl B, **Moore TR**. Abnormalities of Fetal Growth. In Shaffer and Avery's Diseases of the Newborn, 7th Edition. Taeusch HW, Ballard RA, Avery ME, eds. W.B. Saunders, Philadelphia, 1998.
Moore TR. Il liquido amniotico: l'habitat fetale. Ultrasonica XIII:59, 1998.
Moore TR. Diabetes in Pregnancy. In Maternal and Fetal Medicine. Creasy RK and Resnik R, eds. W.B. Saunders, Philadelphia, 1998.
Sohl BD, Scioscia AL, Budorick NE, **Moore TR**. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181(4):898-903.
Moore TR. Pregnancy and hypoxia (editorial comment). Undersea and Hyperbaric Medicine 1999;26(2)59.
Moore TR. Diabetes in Pregnancy. In: Maternal-Fetal Medicine, 4th Edition, Creasy RK, Resnik R (eds). WB Saunders, Philadelphia 1999;964-995.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Yvonne Vaucher, M.D., M.P.H.	Clinical Professor of Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Jackson College, Tufts University, Medford, MA	B.A.	1966	Experimental Psychology
Yale Univ. School of Medicine, New Haven, CT	M.D.	1971	Medicine
Johns Hopkins Univ. School of Hygiene & Public Health, Baltimore, MD	M.P.H.	1993	International Health

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Training and Experience

1971-1972	Pediatric Intern (PL-1), St. Christopher's Hospital for Children, Philadelphia, PA
1972-1973	Pediatric Resident (PL-2), St. Christopher's Hospital for Children, Philadelphia, PA
1973-1974	Attending Physician, Children's Hospital & Health Center, San Diego, CA
1975-1976	Fellowship in Neonatology and Clinical Pharmacology, University of Arizona School of Medicine, Tucson, AZ
1977-1978	Lecturer, Department of Pediatrics, University of Arizona School of Medicine, Tucson, AZ
1978-1983	Assistant Professor of Pediatrics, University of Arizona School of Medicine, Tucson, AZ
1983-1989	Associate Clinical Professor of Pediatrics, Division of Neonatal/Perinatal Medicine, University of California School of Medicine, San Diego, CA
1989-present	Clinical Professor of Pediatrics, Division of Neonatal/Perinatal Medicine, University of California School of Medicine, San Diego, CA
1993-present	Associate, Department of International Health, Division of Health Systems, Johns Hopkins University School of Hygiene and Public Health

Publications (from 1980 to 2000)

1. Haber K, Wachter RD, Christenson PC, Vaucher YE, Sahn DJ, Smith JR. Ultrasonic Evaluation of Intracranial Pathology in Infants: A New Technique. Radiology 1980;134:173-178.
2. Vaucher YE, Walson PD, Morrow G,III. Continuous Insulin Infusion in Hyperglycemic, Very Low Birth Weight Infants. J Ped Gastro Nutr 1982;1:211-217.
3. Branson RS, Vaucher YE, Harrison GG, Vargas M, Thies C. Inter- and Intra-Observer Reliability of Skinfold Thickness Measurements in Newborn Infants. Hum Bio 1982;54:137-143.
4. Vaucher YE, Ray CG, Minnich LL, Payne CM, Beck D, Lowe P. Pleomorphic, Enveloped, Virus-Like Particles Associated with Gastrointestinal Illness in Neonates. J Infect Dis 1982;145:27-36.
5. Vaucher YE, Anna JA, Lindberg RF, Jorgensen EC, Krulich L, Koldovsky O. Maturational Effect of Triiodothyronine and Its Analogue 3,5-Dimethyl-3'-isopropyl-L-thyronine on Sucrase Activity in the Small Intestine of the Developing Rat. J Ped Gastro Nutr 1982;1:427-432.
6. Manthei U, Vaucher YE, Crowe CP. Congenital Diaphragmatic Hernia: Immediate Preoperative and Postoperative Oxygen Gradients Identify Patients Requiring Prolonged Respiratory Support. Surgery 1983;93:83-87.
7. Vaucher Y, Tenore A, Grimes JA, Krulich L, Koldovsky O. Absorption of TSH and ACTH in Biologically Active Form from the Gastrointestinal Tract of Suckling Rats. Proceedings of the International Symposium of Hormones in Milk held in Bratislava, Czechoslovakia, September 1982. Endocrin Exper 1983;17:327-333.
8. Harrison GG, Branson RS, Vaucher YE. Association of Maternal Smoking with Body Composition of the Newborn. Am J Clin Nutr 1983;38:757-762.
9. Vaucher YE, Harrison GG, Udall JN, Morrow G,III. Skinfold Thickness in North American Infants 24-41 Weeks Gestation. Hum Bio 1984;56(4):713-731.

10. Boynton BR, Boynton C, Merritt TA, Vaucher YE, James HE, Bejar R. Ventriculoperitoneal Shunts in Low Birth Weight Infants with Intracranial Hemorrhage: Neurodevelopmental Outcome. Neurosurg 1986;18(2):141-145.
11. Bejar R, Coen RW, Merritt TA, Vaucher YE, Trice J, Centeno R, Gilles F. Focal Necrosis of the White Matter (Periventricular Leukomalacia): Sonographic, Pathologic, and Electroencephalographic Features. AJNR 1986;7:1073-1080.
12. James HE, Boynton BR, Boynton CA, Merritt TA, Vaucher YE, Bejar RF. Severe Intracranial Hemorrhage and Hydrocephalus in Low-Birthweight Infants Treated with CSF shunts. Child's Nerv Syst 1987;3:110-113.
13. Novotny EJ, Tharp BR, Coen RW, Bejar R, Enzmann D, Vaucher YE. Positive Rolandic Sharp Waves in the EEG of the Premature Infant. Neurology 1987;37:1481-1486.
14. Merritt TA, Vaucher YE. Commentary: Infant Follow-Up Programs: Their Impact on Infants and Families. J Dev Behav Pediatr 1987;8:286-287.
15. James HE, Bejar R, Merritt TA, Mannino F, Vaucher YE, Coen R. Insidious Hydrocephalus in the Preterm Newborn following Discharge from the Nursery. Pediat Neurosci 1987;13:129-134.
16. Mahmoud EL, Benirschke K, Vaucher YE, Poitras P. Motilin Levels in Term Newborns Who Have Passed Meconium Prior to Birth. J Ped Gastro Nutr 1988;7:95-99.
17. Vaucher YE. Understanding Intracranial Hemorrhage in Premature Infants: Causes and Developmental Outcomes. Infants and Young Children 1988, 1(2):31-45.
18. Vaucher YE, Merritt TA, Hallman M, Jarvenpaa AL, Telsey AM, Jones BL. Neurodevelopmental and Respiratory Outcome in Early Childhood Following Human Surfactant Treatment. AJDC 1988;9:927-930.
19. Bejar R, Wozniak P, Allare M, Benirschke K, Vaucher Y, Coen R, Berry C, Schragg P, Villegas I, Resnik R. Antenatal Origin of Neurologic Damage in Newborn Infants. Part I. Preterm Infants. Amer J Ob/Gyn 1988;159(2):357-363.
20. Patton S, Huston GE, Jenness R, Vaucher YE. Differences Between Individuals in High-Molecular Weight Glycoproteins From Mammary Epithelia of Several Species. BBC 1989;980:331-338.
21. Mannino F, Heldt G, Vaucher YE, et al (HIFI Study Group). High Frequency Oscillatory Ventilation Compared With Conventional Mechanical Ventilation in the Treatment of Respiratory Failure in Preterm Infants: Neurodevelopmental Status at 16 to 24 Months. J Pediatrics 1990;117(6):939-946.
22. Merritt TA, Hallman MD, Vaucher YE, McFeeley E, Tubman R. Impact of Surfactant Treatment on Cost of Neonatal Intensive Care: A Cost-Benefit Analysis. J Perinatology 1991;10(4):416-419.
23. Hollingsworth DR, Vaucher YE, Yamamoto TR. Diabetic Pregnancy in Mexican-Americans. Diabetes Care 1991;14(3):695-705.
24. Merritt TA, Hallman M, Berry C, Pohjavouri M, Edwards DK, Jaaskelainen J, Grafe MR, Vaucher YE, Wozniak P, Heldt G, Rapola J. Randomized, Placebo-Controlled Trial of Human Surfactant Given at Birth vs. Rescue Administration in Very Low Birth Weight Infants with Lung Immaturity. J Pediatrics 1991;118(4):581-594.
25. Vaucher YE, Gunn J, Gruver M, Meagher C, Bezruchka S. Village Health Status and Attitude Survey in Rural Eastern Nepal: Medical Report from Bala-1991. J Instit Med (Nepal) 1991;13:362-394.
26. Hahn JS, Vaucher YE, Bejar RF, Coen RW. Electroencephalographic Neuroimaging Findings in Neonates Undergoing Extracorporeal Membrane Oxygenation. Neuropediatr 1992;23:19-24.
27. Bejar RF, Vaucher YE, Berry C. Postnatal White Matter Necrosis in Preterm Infants. J Perinatology 1992;12(1):3-8
28. Vaucher YE, Harker L, Merritt TA, Hallman M, Gist K, Bejar R, Heldt GP, Edwards D, Pohjavuori M. Outcome at 12 Months in VLBW Infants With Lung Immaturity: A Randomized, Placebo Controlled Trial of Human Surfactant. J Pediatr 1993;122:126-32.
29. Vaucher YE, Dudell GG, Bejar R, Gist K. Predictors of outcome in candidates for ECMO. J Pediatr 1996;128:109-117.
30. Vaucher YE, Finer NN, Barrington KJ, Gnanaraatnem J. Arterial blood lactate within first 48 hours of life as a predictor of early neurodevelopmental outcome in babies <1500 grams. Pediatr Res 1999;45:199A.
31. Carbine DN, Fein N, Vaucher YE, Speziale M et al. Noenatal CNS injury and developmental outcome after prolonged premature rupture of membranes. Pediatr Res 1999;45:239A.
32. Carpenter S, Vaucher YE, Brownlee A. Cultural transition and infant-feeding practices among Somali immigrant women in San Diego, California. Pediatr Res 1999;45:279A.
33. Finer NN, Tarin T, Vaucher YE, Barrington K. Intact Survival in extremely low birthweight infants after delivery room resuscitation. Pediatr 1999;104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e40.
34. Vaucher YE, Charette V, Boies E, Cataldo J. Cesarean delivery delays postnatal weight gain in healthy, breastfed, term newborns. Pediatr Res 2000;47:437A.
35. Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

Name	POSITION TITLE
Paul R. Wozniak, M.D.	Medical Director, neonatal Services

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
John Carroll University, Cleveland, OH	B.S.	1972-1976	
Stritch School of Medicine, Loyola University of Chicago, Maywood, IL	M.D	1976-1979	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Experience:

1999-Present — Medical Director, Neonatal Services
Sharp HealthCare
San Diego, CA

1995-Present — Chief of Pediatrics
Sharp Memorial Hospital
San Diego, CA

1993-1999 — Clinical Director of Neonatology
Sharp Mary Birch Hospital for Women
San Diego, CA

1990-1995 — Director, Level II NICU
Alvarado Hospital Medical Center
San Diego, CA

1985-Present — Attending Neonatologist
Children's Hospital San Diego
San Diego, CA

1985-Present — Assistant Clinical Professor of Pediatrics
University of California, San Diego Medical Center
San Diego, CA

1984-1985 — Assistant Professor of Pediatrics
University of California San Diego Medical Center
San Diego, CA

PUBLICATIONS

Hallman M, Slivka S, Wozniak P, Sills J: Perinatal development of Myoinositol uptake into lung cells: Surfactant phosphatidylglycerol and phosphatidylinositol synthesis in the rabbit. Pediatric Research, Feb, 1986;20(2):179-185.

Bejar R, Wozniak P, Vaucher Y, Coen R: Antenatal white matter necrosis in newborn infants. Developmental Medicine and Child Neurology, 1986.

Merritt TA, Strayer DS, Hallman M, Spragg RD, Wozniak P: Immunologic consequences of exogenous surfactant administration. Seminars in Perinatology, Jul, 1988 (3): 221-230.

Bejar R, Wozniak P, Allare M, Benirschke K, Vaucher Y, Coen R, Berry C, Spragg P, Villegas I, Resnik R: Antenatal origin of neurologic damage in newborn infants. American Journal Obstetrics & Gynecological, August, 1988; 159(2):357-363.

Vaucher Y, Merritt T, Hallman M, Harker L, Wozniak P, Gist K: Improved outcome following rescue versus prophylactic surfactant treatment in RDS. pediatrics Res 1990; 27:260A

Merritt TA, Hallman M, Berry C, Pohjavuori M, Edwards DK, Jaaskelainen J, Grafe MR, Vaucher Y, Wozniak P, Heldt G, Rapola J: Randomized placebo-controlled trial of human surfactant given at birth versus rescue administration in very low birth weight infants with lung immaturity. Journal of Pediatrics, April, 1991; 118(4):581-594.

Randel RC, Wozniak P, Costa E: The combined use of continuous negative and expiratory pressure and high frequency ventilation for refractory neonatal respiratory distress. Clinical Research 1991;39;11A.

Catanzarite V, Wozniak P, Maida C, Mascarello J, Senac M: Ascites, meconium peritonitis and meconium pseudocyst in a fetus with cystic fibrosis. The Fetus, 1993;3(4);4-5.

Wozniak P, Knight G, Dudell G: ECMO in the treatment of respiratory failure due to neonatal sepsis. Children's National Medical Center Annual ECMO Symposium, Poster Session, Keystone CO, March, 1994.

Seid M, Kurtin P, Romanowski G, Wozniak P, et al. Letter to the editor: Effectiveness of RSV-IG in premature infants: potential pitfalls in clinical settings. Pediatrics, 1998; 101(2);320.

Wiswell TE and the Surfaxin-Lavage for MAS Trial Group. "Bronchoalveolar Lavage with Dilute Surfaxin• (KL_4 Surfactant) for the Management of the Meconium Aspiration Syndrome (MAS)." Pediatric Research 1999;45:326A.

Other Support

HELDT, GREGORY P.

ACTIVE

1 U10 HL64295-01 (Zeiger, Robert) 09/30/1999 - 08/31/2004 %
NIH $572,383
Childhood Asthma Prevention Study (CAPS) for PACRN

The three protocols developed so far are to (1) prevent the development of persistent asthma in preschool children; (2) assess the efficacy of a leukotriene modifier in antibiotics with inhaled corticosteroids; and (3) assess the maximal bronchodilator response in school-age children with moderate/severe persistent asthma.

PENDING

Pending Support

OVERLAP

None

OTHER KEY PERSONNEL (LISTED BELOW) HAVE NO ACTIVE OR PENDING SUPPORT AT THIS TIME.

Neil N. Finer, M.D.
Graham Bernstein, MD
Frank Mannino, M.D.
Yvonne Vaucher, M.D., M.P.H

% = Percentage of Effort

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory: **UCSD:** UCSD Clinical Laboratories have the ability to perform over 800 different medical laboratory tests and procedures at three locations in the following areas: autopsy service, blood bank, chemistry, spec process/phlebotomy, special coagulation lab, hematology, immunogenetics & transplant, microbiology, neuropathology, point of care testing, cytopathology, blood gas lab, rheumatology, surgical pathology, toxicology laboratory, virology, and bone marrow services.

SMBHW: Sharp Mary Birch Hospital for Women (SMBHW) Clinical Laboratory has the ability to perform over 400 in-house medical laboratory tests and an additional 500 tests at three remote locations. Tests are available in the following areas: autopsy service, blood bank, chemistry, spec process/phlebotomy, special coagulation lab, hematology immunogenetics & transplant, microbiology, neuropathology, cytopathology, blood gas lab, rheumatology, surgical pathology, minimal toxicology laboratory.

Clinical: **UCSD:** The core UCSD ISCC is a 40-bed regional neonatal unit which provides full support including cardiac surgery and ECMO with over 550 admissions per year. The obstetrical service in-house delivers approximately 2300 women per year with a very high proportion of high risk and there are approximately 100-120 transports brought into the ISCC at UCSD. This unit cares for approximately 100-110 infants <1500 gms/year, is part of Vermont Oxford Network (VON) and part of the California Perinatal Quality Care Collaboration (CPQCC).

SMBHW: SMBHW is the only free-standing women's hospital in California and the largest delivery service in the State with approximately 7,000 births per year with approximately 800-1200 neonatal admissions/year and 140-160 infants of <1500 gm. SMBHW has a 9911 square foot NICU with 61 beds and is also an active participant in VON and CPQCC. There were 156 maternal-fetal and 192 neonatal transports in 1999.

Animal: N/A

Computer: **UCSD:** There is a neonatal local area computer network within UCSD with access to the hospital information system, PCIS, which includes patient related information including laboratory and diagnostic information and direct internet access, and includes computerized entry and access to all neonatal ventilatory and blood gas data. We have 11 PCs in our administrative offices connected to the main pediatrics server with access to the internet, e-mail and individual computers. We have a dedicated obstetrical computerized information system (Quantitative Sentinel) for detailed charting of maternal and infant information.

SMBHW: The Neonatal Medicine Division has 11 PC's with dual functionality for EMR and Sharp Healthcare intranet. All the beds in the NICU have fully integrated monitoring, charting and reporting functions via CliniComp, EMR and IDX software, which is also, networked with the OB/Perinatal components of the EMR.

Office: **UCSD:** Office space is available at the UCSD Medical Center in the Multipurpose Facility. Neonatology has 10 offices, four full-time, two casual support staff members which includes an office manager, a financial officer, and a data entry coordinator. The facilities include a library and conference room.

SMBHW: SMBHW provides office space for the Neonatal Medical Division as follows: neonatologists (9), clinical nurse specialists (1), nurse practitioners (1), administrative/secretarial support (3), research nurse (1), data acquisition/data analyst (1), programs manager (1).

Other: **UCSD:** UCSD Medical Center provides proximity not only to the neonatal research laboratories, but to the Medical Center Library. As part of UCSD, there is complete access to the medical campus in La Jolla with support from the basic sciences as well as significant epidemiologic and biostatistical support.

SMBHW: SMBHW provides proximity to the Sharp Memorial Hospitals Medical Center Library. As part of the Regional Perinatal System, there is complete access to the UCSD Medical Library in La Jolla.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

UCSD: The UCSD Neonatal Division has 19 Infant Star ventilators, 18 of which have high frequency capability. We have 25 stand-alone oximeters and 9 stand-alone TCM's. Each bedside has full monitoring capability and 16 beds provide trending of all monitored parameters, which includes up to 3 invasive pressures. There is 1 Sensor Medic high frequency oscillator, and 3 EdenTrace II (Mallinckrodt) polysomnogram systems. Specialty gases include nitrogen, NO, and heliox. There are two dedicated blood gas analyzers (Chiron Model #865) equipped to perform basic electrolytes, glucose and lactate.

SMBHW: The NICU at SMBWH has 13 Infant Star ventilators (several with high frequency capability), 5 Bird VIP ventilators, 3 SensorMedics high frequency oscillators, 6 Servo 300A's, and 3 Infant Star Sync ventilators. There are 2 dedicated units for the administration of INO, heliox delivery systems, and every acute care bed has pulse oximetry and transcutaneous oxygen and CO2 monitoring capability. There is a complete monitoring system at each bedside, which includes cardiac, respiratory, non-invasive and multichannel invasive pressure monitoring, and oximetery. Each monitor is connected to the Clinicomp system (computerized medical record system) with the ability to permit graphing of all parameters. There is a dedicated blood gas laboratory located within the NICU, which contains 2 blood gas analyzers (Chiron Model #865 equipped to perform basic electrolytes, glucose and ionized calcium) and an integrated respiratory documentation system.

Introduction and Overview: There have been a number of dramatic improvements in neonatal medicine over the past ten years, which have been introduced following the completion of well-executed prospective randomized trials. These include the current routine use of surfactant for the treatment of respiratory distress which has substantially lowered mortality, and more recently, the use of inhaled nitric oxide to reduce the need for extracorporeal membrane oxygenation (ECMO) in near-term hypoxic neonates. Our neonatology faculty believes that any important future improvements in therapy must be justified by similar approaches, and that the NICHD Neonatal Research Network is the leading organization committed to this rigorous evaluative process.

The Neonatology Program at the University of California, San Diego Medical Center (UCSD) provides direct neonatal care and supervision for the Infant Special Care Center (ISCC) of UCSD at Hillcrest. The mission of this program since its inception in 1969 has been the provision of the highest level of patient care, the teaching and training of pediatricians and neonatologists, and the development and evaluation of improved methods for treating premature and critically ill newborn infants. This academic program has well-established links with the community Neonatal Intensive Care Units (NICU's), including participation in clinical coverage as well as support and encouragement to introduce clinically relevant research activities into these sites. The Perinatal Program at UCSD includes a strong Maternal-Fetal Medicine group, which provides consultation for a large number of high-risk pregnancies within San Diego and is responsible for delivery of the very high-risk maternal population presenting to UCSD. The UCSD Medical School, while relatively young, is now recognized as a major research University ranking #1 in Neurosciences, #2 in Physiology and Bioengineering, #3 in Pharmacology and #4 in Biologic Sciences by the National Academy of Sciences Study of Graduate Education. UCSD is committed to and supportive of both basic and applied research. The UCSD School of Medicine is ranked #11 among all medical schools in NIH grant support, and #4 among public institutions. We would like to enhance our current neonatology program by participating in the NICHD Neonatal Research Network, and believe that our commitment to research and pragmatic innovation will be a positive contribution to this collaboration.

1. Academic Productivity

UCSD Past Involvement in Single and Multicenter Prospective Clinical Trials: UCSD was a principal study site for the NHLBI Division of Lung Diseases sponsored High Frequency Oscillatory Ventilation trial. Dr.'s Mannino, Heldt and Vaucher were active participants not only in the design and conduct of the clinical trial [N Engl J Med 1989 Jan 12; 320(2):88-93] but also in the subsequent neurodevelopmental [J Pediatr 1990;117(6):939-46] and pulmonary [J Pediatr 1990;116(6):933-41] follow-up evaluations. UCSD enrolled 36 of 59 eligible patients in this trial that was conducted in 10 clinical centers, 8 of which were in the USA.

UCSD enrolled 26 of 60 patients in a 2 site trial of human surfactant (N Engl J Med 1986;315:785-90). A subsequent 3-site study evaluated prophylactic versus rescue human surfactant. UCSD contributed over 33% of the patients in this trial which included 246 premature infants (J Pediatr 1991;118:581-94).

UCSD was an active participant the antenatal thyroid releasing hormone (TRH) trial. Dr. T. Moore the Obstetrical PI and Dr. Frank Mannino the neonatologist and lead PI for UCSD, developed a local network which enrolled a total of 117 infants from January 1995 to December 1996 representing 11.7% of the overall 996 infants in this trial which involved 12 US and 1 Canadian centers (N Engl J Med 1998;338:493-8). Fifty-four patients were enrolled from UCSD alone. Ellen Milan, our proposed research nurse, was responsible for the coordination of the local San Diego network and for the completion of patient case report forms at all three sites in San Diego. Of the 54 infants enrolled in the TRH study from UCSD, 52% were Hispanic, 28% White, 16.5% African-American and 3.5% were Asian.

The UCSD neonatology faculty participated in the development of KL4, an artificial surfactant developed by Dr. Charles Cochrane at the Scripps Institute. UCSD was also the principal site for the evaluation of the technique for the administration of KL4. Dr Greg Heldt performed all the in vivo testing in the divisional research laboratories and participated in the primate study to evaluate the potential clinical benefit of this compound [Pediatr Res 1996;39(4 Pt 1):715-24]. The response to KL4 was found to be critically dependent on the level of end-expiratory pressure. A Phase 1 trial followed testing of the efficacy of KL4 in preterm infants with respiratory distress which was conducted at UCSD and 4 others sites [Am J Respir Crit Care Med 1996;153(1):404-10]. UCSD enrolled 9 of the 46 infants in this trial. A clinical protocol for the use of KL4 as a lavage for meconium aspiration was developed following further evaluation in our animal facility (Pediatr Res 1998;43:166A). Our animal laboratory at UCSD was the training site for the initial multicenter trial of KL4 lavage in infants with meconium aspiration (Pediatr Res 1999;45:326A). UCSD and the Children's Hospital and Health Center (CHHC) contributed 6 of the 22 infants in this trial.

The Infant Star ventilator was developed in consultation with the UCSD neonatology faculty. We performed a prospective randomized study to evaluate the effects of synchronous intermittent mechanical ventilation (SIMV) in premature infants and reported improved blood pressure and oxygenation with this technique (J Pediatr 1995;126:407-

11).

We were the principal investigators and the coordinating site for a multicenter trial conducted in 6 centers that was designed to evaluate the potential benefit of synchronous mechanical ventilation. The results demonstrated improved growth and less oxygen dependency at 36 weeks gestation (J Pediatr 1996;128:453-463). UCSD enrolled 90 of the 327 patients (27.5% of total, 49% Hispanic, 22% White, 24% African-American, 4% Asian) in this trial over a 2-year period and the UCSD neonatology faculty was responsible for the coordination, data collection, analysis, and manuscript preparation for this study.

Dr. Frank Mannino, in collaboration with our blood bank director, Dr. Tom Lane, developed a single donor treatment program using multiple small aliquots from a single donor and compared this to standard transfusion practices for neonates requiring blood transfusions. They demonstrated that such a program reduced the number of donor exposures of such infants in our ISCC (J Pediatr 1994;125:92-6).. More recently, in a small prospective trial this group randomly assigned infants to receive either white cell-reduced or non-white-cell reduced irradiated blood. They found that the lymphocyte counts in both groups were significantly increased after transfusion, and there was a significant increase in lymphocytes expressing CD45RA, CD3-/CD16+CD56, CD80, and CD3-/DR on day 14 [Transfus 2000 Jan;40(1):25-34].

Industry Sponsored Studies: UCSD participated in the prospective granulocyte colony stimulating factor (gCSF Filgrastim, Amgen) trial in neonates with thrombocytopenia, sponsored by Amgen and enrolled 11 infants, of whom 45% were Hispanic, 18% White, 27% African-American and 9% Asian. We were a study site for the evaluation of a home monitor in the "I Am Fine" study, enrolling 25 infants in this three center evaluation (Hispanic = 52%, White = 20%, African-American = 28%). Similarly we enrolled 25 infants in a multi-site evaluation of an inline blood gas analyzer of which 56% were Hispanic, 16% were White, 4% were Asian and 24% were African-American, (Via Medical, San Diego, CA).

Observational Studies: This center has described the pulmonary and neurodevelopmental outcomes of infants who required ECMO and demonstrated that the presence of electroencephalographic seizures, burst suppression, clinical status epilepticus, and the presence of chronic lung disease (CLD) were significant predictors of neurodevelopmental sequelae [Neuropediatr 1993 Feb;24(1):19-24, J Pediatr 1996;128:109-17]. Our group was one of the first to demonstrate the relationship between maternal infection and white matter injury in a study of 127 infants of less than 36 weeks gestation. This study found that placental vascular anastomoses in multiple pregnancies, funisitis, and purulent amniotic fluid were the only complications associated with antenatal white matter necrosis [Am J Obstet Gynecol 1988;159(2):357-63].

In collaboration with pediatric neurology and the Center for Research in Language at UCSD our neonatology group has reported on the long-term neurologic and language development of a large cohort of newborn infants with neonatal stroke (J Pediatr 1986;108:459-61).

Recently we have become increasingly interested in neonatal resuscitation, and as a result reviewed the outcomes of extremely low birthweight infants (ELBW) born at UCSD over a recent 4 year period, January 1993 to December 1996 who had received delivery-room (DR), cardiopulmonary resuscitation (CPR). We found, in contrast to the existing current literature, that intact long-term survival was possible and probable [Pediatr 1999;104(4):A1-A4]. In an expanded observational study we collaborated with the Vermont Oxford Network (VON) to review their substantial database from 1994 to 1996 and reported on the neonatal outcomes of 27,707 infants of less than 1500 grams birthweight. We reported that intact neonatal survival without intraventricular hemorrhage was common among such infants following DR-CPR [Pediatr 1999;104(3 Pt 1):428-34]. We have developed a prospective evaluation project to review the actual conduct of neonatal resuscitation using video recording, and our evaluation of our first 100 resuscitations will be published in the near future (Pediatrics 2000, in press).

We have evaluated the utility of serum lactate levels in premature infants and correlated their blood lactate levels with their neonatal outcomes (Pediatr Res 1999;45:199A). We have recently completed a prospective study that evaluated the use of CRP, and IL-6 in facilitating the diagnosis of bacterial sepsis versus line contamination in very low birthweight infants (Pediatr Res 2000;47:340A).

Our group has evaluated the role of prolonged rupture of membranes, chorioamnionitis and gestational age in the development of neonatal CNS injury in 238 premature infants. We found that gestational age at delivery was the strongest independent predictor of neonatal CNS injury (Pediatr Res 1999;45:239A).

Dr. Vaucher, et al, have recently determined that the majority of term readmissions to UCSD in the first two weeks after birth are related to inadequate enteric intake associated with difficulty breastfeeding (Pediatr Res 1997;41:212A)

and that breast-fed term infants born following Cesarean section experience greater weight loss and delay in regaining birthweight compared to vaginally delivered infants (Pediatr Res 2000;47:437A).

Currently Active Prospective Multicenter Studies: We are currently participating in a prospective, blinded evaluation of Curosurf® sponsored by Dey Laboratories (Napa, CA). We have enrolled 8 patients since initiation of our site within the past month. We are also participating in the multicenter, multinational randomized trial of hypothermia for hypoxic ischemic encephalopathy sponsored by Olympic Medical (Seattle, WA). UCSD will be a study site in the forthcoming trial to evaluate ibuprofen for the treatment of PDA in preterm infants, sponsored by the Pediatric Pharmacology Research Units (PPRU) and Farmacon-IL, LLC (Westport, CT). We have initiated a prospective, randomized trial in collaboration with Einstein Medical Center in Philadelphia comparing synchronous intermittent mechanical ventilation with high frequency oscillation in extremely low birthweight infants. We have enrolled over 50 infants to date at both sites. We are currently an active site for the Phase 2 study of KL4 surfactant lavage in infants with meconium aspiration. We are currently initiating a prospective randomized blinded study to evaluate the use of a vancomycin-lock technique to reduce nosocomial sepsis in infants of less than 1000 gm with central venous lines.

For all of our past and current studies, approximately 50% of enrolled infants have been of Hispanic origin. This percent remains applicable for our ongoing studies, with all of our enrolled infants in the Hypothermia Study to date being of Hispanic origin, and 55% of infants in the Curosurf study and the SIMV versus HIFI study enrolled to the present being Hispanic.

Sharp Mary Birch Hospital for Women (SMBHW): Past Involvement in Single and Multicenter Prospective Clinical Trials: SMBHW has participated in a number of surfactant studies, usually as a co-site with CHHC including the comparative study of prophylactic versus rescue human surfactant (J Pediatr 1991;118:581-94), the original Exosurf® trials, and the multicenter study of surfactant in term infants with respiratory failure (J Pediatr 1998;132:40-47). The SMBHW Neonatology Unit was one of 15 in the Phase 2 trial of the effectiveness and safety of KL4- surfactant lavage in meconium aspiration (MAS). The unit is participating in the current Phase 2 KL4 lavage trial for meconium aspiration (Site PI, Dr. G. Bernstein) and has already enrolled 1 lavage patient in this study, which was initiated in the past month. SMBHW is currently the most active study site for the randomized multicenter comparison of Curosurf® and Survanta® in the treatment of established neonatal respiratory distress syndrome. SMBHW has enrolled 13 of the total of 76 infants enrolled at the time of this writing.

SMBHW was also a site for the double blind randomized placebo controlled safety and efficacy study of g-CSF (Amgen) in the treatment of late onset of neonatal sepsis.

SMBHW participated in the Inhaled Nitric Oxide in infants with persistent pulmonary hypertension, a two-site study involving SMBHW and Loma Linda University (Site PI, Dr. Maynard Rasmussen). This study was completed in 1999 and is being prepared for publication.

SMBHW is actively involved in a multicenter comparison of platelet mass index versus platelet counts as predictors in thrombocytopenic patients (PI, Dr. Christensen, University of Florida).

The Maternal Fetal Medicine program at SMBHW has been involved in a number of multicenter collaborative projects and participated in the protocol of Home Uterine Monitoring of Women at Risk for Preterm Labor sponsored by the CareLink Corporation in 1991. The objective of this multicenter randomized clinical trial was to compare the safety and efficacy of the CareFone Home Uterine Monitor to standard methods of uterine activity assessment (self-palpation and observance for other signs of labor) in patients at risk for preterm delivery. The SMBHW and Sharp Perinatal Center were added as an additional study site to increase subject enrollment after the project had been in progress at 8 other sites for over 18 months. In the 40-day interval between April 28 (our start date) and June 7, 1991 (conclusion of the study), 30 San Diego patients were enrolled in this collaborative trial. Of this group, 27 (90%) completed the protocol with 100% complete data. The ethnic/racial composition of these patients included 6 Hispanics, 2 African-Americans, 1 Asian, 16 White, and 2 others.

Dr. Catanzarite (project site coordinator) and the Sharp Perinatal Center staff participated in the CareMark Home Uterine Activity Monitoring trial completed in 1994. The objective of this collaborative, multicenter study was to compare home uterine activity monitoring with a sham monitoring of uterine activity. Sharp Perinatal Center was added as an additional site to increase enrollment after this double-blind, randomized study was already in progress. Over the last five months of the enrollment period, 21 patients were registered and 20 (95 %) of these subjects went on to complete the study. As in the CareLink study, auditing of the study data revealed 100% data completion. The ethnic/racial composition of this group included 7 Hispanics, 2 African-Americans, 1 Asian and 11 Caucasian women.

SMBHW was selected as a sampling site for the study of Prevalence and Magnitude of Perinatal Substance Exposures in California conducted in 1992 and 1993. Dr. Marianne Weiss was the San Diego site coordinator for the

multicenter collaborative study that required submission of patient specimens and anonymous collection of descriptive information on all pregnant women admitted to the hospital. Over a two-month period more than 700 consecutive cases were enrolled (N Engl J Med 1993;329:850-54).

Dr. Catanzarite (project site coordinator) and the physicians from Sharp Perinatal Center are currently participating in the multicenter study of the Use of the Labor Assister System in Nulliparous Women with Epidural Analgesia during the Second Stage of Labor. The Labor Assister system was designed to provide an external, controlled, secondary force to assist women during the second stage of labor. This prospective, randomized, sham controlled, multicenter study will evaluate if women who use the Labor Assister System have a lower incidence of operative delivery compared to women assigned to the use of a sham device. SMBHW was selected as the second of five sites currently conducting the study. After enrolling patients more rapidly than expected and completion of the initial commitment to enroll 150 patients in the first year, SMBHW has been asked to continue to enroll additional patients to supplement enrollment at other sites with slower patient accrual. Study sponsors have recognized SMBHW as having excellent study nurses with high protocol compliance, low case report form error rates, and excellent source documentation.

2. Neonatology Staffing: Dr. Neil Finer is Director of the Neonatology Medicine Program at UCSD and Dr. Frank Mannino is Clinical Director of the Infant Special Care Center (ISCC). Dr. Yvonne Vaucher is Director of the Neurodevelopmental Follow-up Program (ISCFU) at UCSD.

The UCSD Neonatology Program has always worked collaboratively with other neonatology programs in San Diego including the SMBHW facility, currently the largest in-born perinatal hospital in California.

The Neonatology Medicine Division at UCSD currently consists of four full-time academic faculty members with recruitment underway for a fifth individual who has demonstrated expertise in translational research. We have experienced faculty who have independent, but complementary research interests. All of the faculty have collaborated in the conduct of single and multicenter clinical trials. In addition there is a very close working relationship with our perinatal and maternal/fetal medicine specialists, resulting in a continuum of care for the high-risk mother and her infant. We have developed a consortium arrangement with SMBHW, which will significantly increase the enrollment of patients into Network prospective trials and contribute to the Network generic database. There are 9 full-time Board Certified neonatologists on staff at SMBHW under the Direction of Dr. Paul Wozniak, and a very active Maternal-Fetal Medicine Unit. As a group, they have agreed to participate under the direction of Dr. N. Finer for all activities relating to Neonatal Research Network (see Letters of Support). Dr. Graham Bernstein, a former faculty member at UCSD Medical Center who relocated to SMBHW in 1999, to support neonatal clinical research activities at SMBHW, will be the site PI for SMBHW.

Dr. Neil Finer: The current Chief of Neonatology at UCSD, Dr. Neil Finer relocated to this position 5 years ago. He has an established 25-year track record of clinical and related animal research in neonatal medicine and in developing and expanding the evidence basis of neonatal practice. He has been instrumental in designing and conducting multicenter trials and has always been committed to the training of fellows in neonatal medicine. Dr. Finer's previous clinical research accomplishments include controlled studies evaluating the role of chest physiotherapy in the neonate (Pediatr 1978;61:282-285, Can Physiother Assoc 1989;30:12), a prospective trial to evaluate the role of Vitamin E in retinopathy of prematurity (Lancet 1982;1:1087-1091, Ophthalmol 1983;90:428-35), and prospective population studies to evaluate the factors which predicted outcome in near-term infants with hypoxic ischemic encephalopathy (Am J Dis Child 1983;137:21-25) including the evaluation of clinical predictors of outcome through the follow-up of a large cohort of such infants to school age and later childhood (Dev Med Child Neurol 1985;27:473-484, J Develop Behav Pediatr 1988;9:298-306). He completed prospective studies evaluating the physiologic effects of endotracheal intubation and the role of premedication including muscle paralysis (J Pediatr 1984;104:303-309, Crit Care Med 1989;17:1293-1296). His interest in apnea of prematurity has included studies which objectively evaluated the presence of neonatal apnea, and the difficulty experienced in diagnosing this disorder in the clinical environment (Pediatr 1988;82:713-720) the physiologic correlates of different apnea types (J Pediatr 1992;121:943-950) and the effect of specific agents used to treat such apnea (J Pediatr 1988;112:115-21, J Pediatr 1986;108:124-129). He co-organized and completed one of the few prospective randomized placebo controlled trials to evaluate and compare such treatments (J Pediatr 1990;116:648-653.).

Dr. Finer was one of the first neonatologists to utilize fiberoptic bronchoscopy to assist in the diagnosis and treatment of airway abnormalities in neonates (Pediatr Pulmonol 1989;7:116-120, Pediatr Pulmonol 1992;12:48-51) and has performed over 350 neonatal bronchoscopic procedures to date. In 1988, Dr. Finer introduced ECMO into Canada and developed the first Canadian ECMO program. He and coworkers subsequently described short and long term outcomes of infants who received ECMO (CMAJ 1995;152:1981-1988, Early Hum Dev 1996;44:3;225-33), the value of venovenous ECMO with jugular cannulation (J Pediatr Surg 1996;31:1391-5), and recently collaborated in the

production of a cost analysis of ECMO [Crit Care Med 2000; 28(3):872-8]. He described the value of predictors of outcome including lactate in such high-risk near-term neonates (CMAJ 1992;146:501-508, JSOGC 1994;16:1909-1916, J Pediatr 1994;125:763-768]. Dr. Finer was the principal investigator for a comparative Canadian Multicenter study of a new animal-derived surfactant (bovine lung extract, Bles®), which was funded by the Canadian Medical Research Council (Pediatr Res 1998;43:293A).

In the early 1990's, Dr. Finer became interested in the role of inhaled nitric oxide (INO) and evaluated its efficacy in the animal laboratory (Pediatr Res 1994;35:15-19) and then completed a prospective trial to compare the use of different doses of INO in the hypoxic near-term neonate (J Pediatr 1994;124:302-308). He then became the principal investigator for the Canadian Inhaled Nitric Oxide Study Group (CINOS) and began a multicenter prospective trial to evaluate inhaled NO funded by the Canadian Medical Research Council. This group was invited to join with the NICHD Neonatal Research Network and form the NINOS collaborative of which Dr. Finer remained Co-PI with Dr. Richard Ehrenkranz. This collaboration resulted in NINOS manuscripts describing the results of the use of INO in near-term hypoxic neonates with (Pediatr 1997;99:838-45) and without congenital diaphragmatic hernia (CDH) (N Engl J Med 1997;336:597-604) and the long-term follow-up of these infants (J Pediatr 2000;136:611-7). These studies were instrumental in the approval of INO as a therapeutic option for near-term infants by the FDA in December, 1999. Dr. Finer is currently the principal reviewer for the Cochrane Library for studies regarding INO in near-term and term neonates and preterm neonates (Cochrane Libraries Issue 1, 2000 Oxford Update Software). Dr. Finer was the original author of a protocol on the use of antenatal steroids for fetal CDH, a study that is currently being initiated by the CDH Registry.

Since relocating to UCSD in 1995, Dr. Finer has completed a number of single-center studies, which have included the non-invasive use of ventilatory support techniques including nasal synchronous intermittent mechanical ventilation (Pediatr Res 1999;45:184A, J Pediatrics 2000, in press). The preliminary results of a single center study comparing low dose and high dose NO were presented last year (Pediatr Res 1999;45:184A). Dr. Finer initiated and completed observational studies in collaboration with VON to evaluate the outcome of infants who required DR-CPR as described above. Dr. Finer and the neonatology group at UCSD have subsequently developed the first video-recording system to assess the actual conduct of neonatal resuscitation (Carbine, et al Pediatrics 2000, in press), and they are now initiating further research to assess the value of different resuscitation interventions. Dr. Finer is a member of the Steering Committee for the KL4 studies involving infants with meconium aspiration and is the co-PI with Dr. Mannino for this study at UCSD.

Dr. Finer and Dr. Mannino have been the principal representatives of UCSD Medical Center in the VON sponsored quality assurance project (NIC/Q-2000). UCSD is one of 35 units in the USA to participate in this project that has focused on the evaluation of current neonatal care. As a result of participation in this initiative, we are currently conducting a prospective, blinded, randomized evaluation of the vancomycin lock technique, and have completed a systematic review of the use of low dose vancomycin to prevent nosocomial sepsis (Craft A, Finer NN, Barrington KB. A systematic review of vancomycin prophylaxis for neonatal nosocomial sepsis. Cochrane Library 2000, Issue 1).

Dr. Finer has recently been recently appointed to the Neonatal Drug Trials Task Force of the PPRU of which UCSD has been an active member. Thus it can be seen that Dr Finer remains committed to the prospective evaluation of potentially useful therapeutic interventions, and is able to design, conduct and complete both single center and multicenter projects at his previous and current academic positions. Dr. Finer is currently a tenured Professor-in-Residence and a Vice-Chair in the Department of Pediatrics at UCSD. He was the first President of the Neonatal Section of the Canadian Pediatric Society and is currently Vice-President and President-Elect for the California Association of Neonatologists. Dr. Finer will be the Principal Investigator and will supervise all aspects of work related to the NICHD Neonatal Network. The requested salary support represents 10% effort as stipulated, although Dr. Finer anticipates contributing at least [%] of his time to work related to NICHD Neonatal Network.

Dr. Frank Mannino: Dr Mannino is the Medical Director of the ISCC and of the Neonatal Respiratory Therapy department at the UCSD Medical Center. He has been at UCSD since 1974. He has an established record of leadership and participation in multicenter prospective randomized trials. His research interests have included surfactant biochemistry and replacement, and mechanical ventilation for neonates including the critical evaluation of newer modalities including high frequency ventilation, and synchronized intermittent mechanical ventilation. Dr. Mannino was a key participant in the original early studies of human surfactant, harvested from amniotic fluid. More recently he became involved in the development and testing of the synthetic surfactant KL4 and is the co-PI at UCSD for the study of KL4 as a lavage in infants with meconium aspiration and a member of the Steering Committee for this trial. His input

has included the teaching of the lavage technique to representatives of at least 35 others sites using the neonatal animal research laboratories at UCSD.

Dr. Mannino is an acknowledged expert in the use of high frequency oscillatory ventilation (HFO). He was a member of the Steering Committee for the original NHLBI funded HIFI trial and the PI for the UCSD site. For this study Dr. Mannino provided an animal laboratory evaluation of the ventilator chosen for this trial (Hummingbird), and designed the patient circuit to be used in this trial. Subsequently, he was instrumental in the design and testing of a new ventilator which combined conventional ventilation with HFO (Infant Star), and later, along with Dr. G. Bernstein and Dr. Heldt, he assisted in the design and subsequent testing of an aplanation technique for synchronizing ventilation. This group then planned and conducted the prospective trial to compare SIMV versus conventional ventilation. Dr. Mannino was the site PI for the prospective randomized trial of antenatal TRH. He was able to develop a consortium arrangement including the Balboa Naval Hospital, and the Kaiser Hospital and the San Diego site enrolled 117 infants into this trial. Dr Mannino served as a consultant to the federally funded Birth Place grant "A Prospective Study of an Out-of-Hospital Birth Center" (Grant #RO1-HSO07161, AHCPR). He was the organizer and PI of the prospective study to evaluate single donor transfusions in a study which demonstrated the safety and efficacy of using a directed donor unit multiple times to decrease donor exposure of very premature infants. Dr. Mannino is currently the co-PI with Dr. Finer for the Olympic head cooling study for infants with hypoxic ischemic encephalopathy. Over the past 18 months, Dr. Mannino has been the Co-PI with Dr. Finer for the UCSD site in the VON NIC/Q-2000 project, involving 35 NICU's. He has developed a number of rapid cycle improvement projects within VON that have been focused on reducing the nosocomial sepsis rate in our ELBW infants. This has involved changing our approach to percutaneous central lines, and the development of new protocols for skin preparation, the use of hyperalimentation, and blood culture techniques. This multidisciplinary aspect of this project has improved our internal collaboration, and further streamlined the processes of care in our unit. Dr. Mannino and Dr. Vaucher were collaborators with the diagnostic ultrasound group project on 3-Dimensional Imaging of the Neonatal Brain in High Risk Neonates. The accuracy and reliability of this technique was recently evaluated in a study of 30 neonates (J Ultrasound Med 2000, in press). He is the Chairman of the California Children's Services (CCS) subcommittee on Neonatal Care, a position he has held for the past 4 years. In that capacity he evaluates and reviews the performance of NICUs throughout the state, and has a broad view of current neonatology practices. In addition, he is instrumental in developing the standards for neonatology care in California.

Dr. Yvonne Vaucher: Dr. Vaucher is a neonatologist with a long-standing interest in neurodevelopmental outcome of high-risk infants. Since 1984 she has been the director of the UCSD Infant Special Care follow-up (ISCFU) program and is responsible for all aspects of neurodevelopmental follow-up and evaluation for UCSD NICU graduates. In 1993, Dr. Vaucher was awarded a Masters in Public Health from John Hopkins University School of Hygiene and Public Health. She contributes expertise in epidemiology, database management, and statistical analysis to all divisional research projects and clinical trials and is experienced in the use of various databases and statistical analysis software (e.g., EPI INFO, dBASE, SAS and SPSS).

As ISCFU director, Dr. Vaucher developed a computerized database that includes demographic and neurodevelopmental outcome data for every high-risk infant enrolled in the follow-up program since 1989. Dr. Vaucher is primarily responsible for design, data collection, management and statistical analysis of all neonatal neurodevelopmental outcomes research at UCSD. Dr. Vaucher and colleagues have described the outcomes of infants who required ECMO (J Pediatr 1996;128:109-17, Neuropediatr 1992;23:19-24). They also noted that among ECMO survivors, feeding difficulty in the neonatal period was associated with subsequent language delay in early childhood (Pediatr Res 1991;29:259A).

Dr. Vaucher followed up the first cohort of infants to receive human surfactant (J Pediatr 1993;122:126-32). In conjunction with Dr. Raul Bejar and her colleagues at UCSD, Dr. Vaucher described the perinatal epidemiology of antenatal and postnatal white matter injury, including the association between perinatal white matter injury and maternal chorioamnionitis and placental anastomoses in monochorionic/diamnionic twin gestations (AJNR 1986;7:1073-1080). Dr. Vaucher reported adverse neurodevelopmental outcomes associated with white matter injury including post-natal ventricular dilatation (Pediatr Res 1988;23:458A, Pediatr Res 1987;21:405A) cystic lesions (Pediatr Res 1987;21:405A), EEG abnormalities (Neurol 1987;37:1481-1486), and early ventriculoperitoneal shunt placement for post-hemorrhagic hydrocephalus [Pediatr Neurosci 1987;13:129-134, Neurosurg 1986;18(2):141-145]. Dr. Vaucher also described the association between maternal diabetes in pregnancy and hypotonia and motor delay in infancy [Diab 1990;39(1):302A] and recently participated in an observational study which noted the lack of association of initial arterial blood lactate levels in VLBW infants with early infant outcome (Pediatr Res 1999;45:199A).

Dr. Vaucher and colleagues have performed a number of retrospective case-control studies in collaboration with Dr. Kurt Benirschke and described the independent adverse effect of congenital syphilis on neurodevelopmental outcome in

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preterm infants (Pediatr Res 1996;39:283A), the increased risk of white matter injury in infants born to mothers with maternal floor infarction of the placenta (Pediatr Res 1998;43:204A), and the similar neurodevelopmental outcome in preterm survivors of twin-twin transfusion compared to gestational age matched twins without placental vascular connections (Pediatr Res 1996;39:283A). They also reported the effect of expectant management of premature rupture of membranes at less than 32 weeks gestation on neonatal brain injury and neurodevelopmental outcome [J Invest Med 1999;47(2):90A, Pediatr Res 1999;45:239A]. Dr. Vaucher and Dr. Finer performed a case-control analysis comparing ELBW survivors of delivery room CPR survival with comparable non-CPR ELBW infants and demonstrated similar neurodevelopmental outcomes [Pediatr 1999;104(4) url: www.pediatrics.org/cgi/content/full/104/4/e40]. Dr. Vaucher has also reported the importance of inadequate enteric intake in term, breastfeeding infants as the underlying cause of neonatal hospital readmission (Pediatr Res 1997;41:198A, 212A), and has recently described the association between Cesarean section delivery and delayed postnatal weight gain in healthy breastfed infants (Pediatr Res 2000;47:437A).

Dr. Gregory Heldt: Dr. Heldt is board certified in both neonatology and pediatric pulmonology and has a continuing interest in neonatal pulmonary physiology. Before coming to San Diego in 1985, he was the Director of the Pediatric Pulmonary Function Laboratory, Cardiovascular Research Institute, University of California, San Francisco (UCSF). Dr. Heldt developed methods for measurement of pulmonary function in young children, and for the evaluation of exercise performance for follow-up studies. He has been actively involved in the production and clinical evaluation of pulmonary surfactant as a clinical therapy. In addition, Dr. Heldt has been involved in the development of KL4, including the original animal studies evaluating its effects, and the subsequent clinical trials. Dr. Heldt is in his sixth year as a member of the UCSD IRB.

While at UCSF, Dr. Heldt helped to design the original clinical trials of both prophylactic and rescue Exosurf® treatments. He performed the initial measurements of lung mechanics and functional residual capacity in infants in both trials, both in the delivery room during initial dosing and resuscitation, and subsequently in the NICU. These initial studies were eventually expanded into the multicenter collaborative protocols implemented by Burroughs-Wellcome.

Dr. Heldt was the co-Principal Investigator for the San Diego center in the HIFI trial sponsored by the NHLBI. He participated in the trial design, especially for the follow-up studies, the implementation of the protocol, and data interpretation. He was also responsible for the follow-up studies of pulmonary function in the study infants. This involved developing a computerized pulmonary mechanics measurement system, a nitrogen washout method for FRC, and a hypoxic challenge (J Pediatr 1990;116:933-41).

Dr. Heldt was a co-investigator with Dr. A. Merritt in the randomized prospective trial comparing prophylactic versus rescue human surfactant at 3 sites, including UCSD (J Pediatr 1991;118:581-94). He assessed pulmonary mechanics and the effect of surfactant on the patent ductus arteriosus in 61 patients included in the original study (Pediatr Res 1989;25:305-10). From 1988 to the present, Dr. Heldt has been involved in the development of the artificial surfactant, KL-4. He was responsible for the in-vivo assays of all formulations of the KL-4 surfactant, using a preterm rabbit model. His laboratory research had direct implications for the clinical studies that followed, including the effect of the viscosity of various formulations on the improvement in lung compliance, the effect of dose volume, the efficacy of prophylaxis versus rescue treatment, the adjunctive use of high-frequency ventilation, and the distribution of KL-4 in the lungs. Dr. Heldt's participation in the laboratory research with rhesus monkeys at the California Primate Facility, University of California, Davis (UCD) helped determine many aspects of the final clinical protocol. Dr. Heldt was the Principal Investigator of the Phase I/II safety and efficacy trial of the KL-4 surfactant in premature infants with respiratory distress syndrome (RDS) at UCSD. He helped to design the clinical protocol and the application to the FDA. UCSD enrolled 9 of the 46 infants (five centers) [Am J Respir Crit Care Med 1996;153(1):404-10]. At the present time, he is working with Discovery Laboratories in designing a prospective, blinded Phase III multicenter trial of the KL-4 surfactant compared to a commercially available surfactant for infants less than 1750 with RDS. We expect to begin enrollment in the Fall 2000, and project that we will recruit 60-70 infants at this center. Dr. Heldt is also involved in the design and conduct of the KL-4 studies for meconium aspiration

Dr. Heldt is presently a co-investigator in the first year of a five-year, five-center Children's Asthma Research and Education (CARE) Network, sponsored by the NHLBI. The first three protocols in this network include:

A. Prevention of Early Asthma in Kids (PEAK). A study of 270 children, ranging in age 18-30 months in the next 18 months, and will be testing the hypothesis that daily inhaled corticosteroids (ICS) will prevent the development of asthma at age 4-6 years in wheezy infants.
B. Comparative Efficacy of a Leukotriene Antagonist and an Inhaled Corticosteroid in Children with Mild to Moderate Persistent Asthma (CLIC). This study will involve 210 children aged 6 to 18 years with mild to moderate persistent

asthma who will be randomized to one of two cross-over treatment schedules to receive a) leukotriene receptor antagonist interspersed with placebo washout, or b) ICS or placebo.

C. Maximizing and maintaining Asthma Control in Moderate to Severe Persistent Allergic Asthmatic Children with Severe Bronchial Obstruction (MAX). This study will involve 88 children aged 8 to 16 years with poorly reversible lung function requiring ICS therapy. They will be randomized to a masked, placebo-controlled trial to determine if bi-monthly injections of anti-IgE or placebo (each with inhalation of active salmeterol) reduce ICS requirements and improves lung function.

As a member of the Equipment Committee, Dr. Heldt is helping to develop the methodology for pulmonary function testing in the children 2-4 years of age, standardization of spirometry and peak flow testing, methacholine challenge, design of data forms, implementation of the local data base which will be directly linked to the Data Coordinating Center, the development of a Manual of Operations, and interpretation of the clinical and pulmonary function test data.

In addition to the multicenter trials described above, smaller protocols will be implemented for development of infant pulmonary function testing, primarily using impulse oscillometry and partial flow-volume loops, and measurement of chest wall and diaphragmatic function. We anticipate that many of these techniques will be useful in evaluating pulmonary function in infants in the nursery, and for follow-up studies of infants treated with new modalities during newborn intensive care.

Dr. Heldt is presently a co-investigator on a Small Business Innovative Research (SBIR) grant from the NHLBI, in collaboration with Jaycor Corp., San Diego which involves the development of a non-contacting acoustic sensor for the detection of respiratory and body movement. We have shown that the device can accurately detect central apnea in preterm infants, and can distinguish between general body movements and respiratory movements. We are in a Phase I feasibility to use the sensor as a trigger for synchronized intermittent mandatory ventilation, with improved response time over ventilators using airway flow or abdominal pressure capsule sensors. We have studied more than 60 infants of all sizes, both on and off mechanical ventilation. We will be applying for three-year Phase II funding, which will bring the sensor to the product stage. This project represents our Division's ongoing collaboration with industry to develop innovative new methods of respiratory care.

Dr. Graham Bernstein: Dr. Graham Bernstein completed his training in Neonatology at UCSD and joined the faculty in 1989. He developed an interest in synchronized intermittent mandatory ventilation during his training, and was instrumental along with Dr. Mannino and Dr. Heldt, in developing the synchronization module for the Infant Star ventilator, and is very knowledgeable on all forms of available ventilator synchronization and the use SIMV, (Crit Care Med 1995;23:1739-44). He completed a number of studies demonstrating the benefit of SIMV on improving tidal volumes and oxygenation [J Pediatr 1995;126(3):407-411, Am J Resp Dis Crit Care Med 1994;150:1444-1448], and was the principal investigator for the prospective multicenter randomized trial to evaluate SIMV in premature neonates [J Pediatr 1996;128(4):453-463]. In 1999 Dr. Bernstein relocated to SMBHW to become the Director of their Neonatal Respiratory Care Department, and to provide leadership and expertise for broadening the involvement of SMBHW in prospective clinical trials. Dr. Bernstein will be the site Principal Investigator for SMBHW for our participation in the Neonatal Research Network.

Neonatal Research Laboratories: The UCSD Division of Neonatology has two separate animal facilities in the Clinical Teaching Facility with a total of 1,000-sq. footage. The laboratories are equipped to perform physiologic research and contain two overhead radiant warmers, an Infant Star #950, 2 Baby Bird ventilators, a Healthdyne infant ventilator, and three computers equipped to perform continuous physiologic data acquisition. In addition the lab is equipped with a fluorometer providing the capability of utilizing microspheres to determine cardiac output and regional blood flow distribution. Cardiac output can also be measured with a thermistor catheter (Edwards Laboratories). We are capable of performing continuous physiologic monitoring for heart rate, respiration, pulse oximetry, pulmonary and systemic artery pressures, and end-tidal CO2. The laboratory is equipped with two Corning 288 complete blood gas analyzers capable of measuring electrolytes and blood gases. In addition, we are able to perform full lung mechanics utilizing a special purpose-built body plethysmograph on very immature animals. We have currently added the capability of creating pleural windows to evaluate and measure distribution of aeration by computerized video microscopy and fractal analysis. We have utilized these laboratories to train investigators from over 30 different sites for the previous trials of high frequency ventilation, synchronized intermittent mechanical ventilation, and bronchial lavage technique for the KL-4 meconium study. We also use this facility to provide a training laboratory environment for the teaching of the use of clinical high frequency ventilation using the Infant Star ventilator, and to date have trained over 200 individuals from the USA, Australia, Europe, and Asia.

3. Available Population and Perinatal Data Systems: The UCSD Medical Center currently serves a disproportionately high-risk population with approximately 2300 high-risk deliveries per year. This hospital was the site of the previous county hospital and remains the primary institution providing care for the indigent population of San Diego. We have detailed computerized databases for both our obstetrical and neonatal populations at both centers. The neonatal database at UCSD also includes a unique information set regarding all aspects of respiratory support. This database contains all blood gases, with the associated ventilator settings, as well as information about the level and duration of respiratory support for each infant cared for within the ISCC. Approximately 560 infants are admitted to the ISCC at UCSD each year, with 105-110 having a birthweight of less than 1500 gms. Transports represent approximately 120 admissions per year, or approximately 20% of total admissions. Table 1 demonstrates patient related information from our unit for the past 3 years including some of the information from our associated respiratory database.

The delivery population at UCSD is approximately 67% Hispanic. The racial and ethnic mix of the infants admitted to the ISCC at the UCSD Medical Center is as follows: Hispanic = 50%, African-American = 17%, White = 29%, Asian= 3%, and Other = 1%. Thus our patient population has a higher representation of Hispanic mothers and infants than California overall (44%). The payor mix also reflects the fact that UCSD continues to be the principal hospital in San Diego serving our indigent population. The UCSD ISCC payor mix for 1999-2000 was self-pay/uninsured (17%); Contracted 42% [capitated (12%); IPA non-contracted (9%); contracts (21%)]; and MediCal (41%).

In 1999, UCSD Medical Center delivered 2224 babies, 38 twin sets and 2 triplet sets. Ninety one pregnancies were less than 28 weeks gestation, or approximately 4% of deliveries, and 125 were less than 1500 gm, 5.6% of deliveries, representing 4 times the state and national averages. There were 31 infants with a cord pH < 7.1, or 14 per 1000 deliveries and 47 infants with a 5 minute Apgar score < 7, 2.% or 21 per 1000 deliveries. There were 136 diabetic pregnancies, and 134 mothers with pre-eclampsia or HELLP syndrome, for an incidence of each of these complications of 60/1000 deliveries. The primary Cesarean section rate was 17.5% (390) and the secondary Cesarean rate was 8.4%, for an overall Cesarean section rate of 26%. The stillbirth rate was 13.4 per 1000 deliveries.

We have developed a consortium arrangement with SMBHW, the only freestanding Women's Hospital in the State of California, and 1 of only 10 in the USA. The SMBHW has an active and academic Maternal Fetal Medicine Program directed by Dr. D. Schrimmer with the Clinical Director of Perinatal Medicine being Dr. L. Cousins.

As of the last OSHPD dataset, SMBHW is currently the largest delivery hospital in California, and delivered 7007 infants in 1999 of which there were 128 twin sets and 8 triplets; 125 babies were less than 1500 gms birthweight, representing 1.8% of all deliveries. The primary Cesarean-section birth rate was 17.9% and the repeat Cesarean-section rate was 9.8% for an overall rate of 27.8%. A five minute Apgar score of <6 occurred in 0.8% of all deliveries and 2.2% of all women had not received prenatal care. Stillbirth rates were 4.4% per 1,000 deliveries in 1999. In addition, as the Tertiary care maternal- neonatal hospital in the Sharp system in San Diego, this hospital receives all high risk pregnancies from the other three Sharp Hospitals, Grossmont, Sharp Chula Vista and Coronado. In 1999 these 4 hospitals delivered 12,533 infants.

SMBHW has a 61-bed NICU with approximately 1250 admissions/year, admits approximately 150 infants of <1500 gm, and is also a participant of VON and California Perinatal Quality Care Collaborative (CPQCC). The neonatal patient related information over the past 3 years from SMBHW is shown in Table 2. Approximately 17% of admissions to SMBHW are transfers. The racial mix of patients cared for at SMBHW is: Hispanic 30%, White 40%, African-American 15 %, Asian 12%, Native American 1%, and 2% Others. Their payor mix is MediCal 47%, Contracted 52%, and uninsured of 1%.

Thus overall, the patient population numbers for our combined centers represent a total of 1810 admissions/year, of which approximately 260 are VLBW infants, with approximately 120 infants of 1000 gm or less.

4. Maternal Fetal Medicine Programs

In-Patient Obstetrical Facilities: UCSD Medical Center: All UCSD's obstetrical inpatient activity occurs at UCSD Medical Center located in the Hillcrest area of San Diego. It consists of 3 operating rooms, 13 labor-delivery rooms, a 3-bed recovery room, 2 triage beds, and 24 postpartum/antepartum beds. The Main Operating Room and Surgical Intensive Care Unit are on the same floor and within 30 yards of the delivery unit. Full-time obstetrical anesthesia services are provided, and one of the labor rooms is outfitted specifically for invasive hemodynamic monitoring. All the delivery/operating rooms, as well as one additional labor room, are capable of caring for critically ill gravidas. All rooms are equipped with electronic fetal monitoring networked to a server and displayed on multiple PC-based monitors. An electronic labor record is maintained with noninvasive maternal and fetal vital signs available. An ATL Ultramark-1000 ultrasound machine and an ATL Ultramark-IV ultrasound machine are kept on Labor and Delivery for

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Table 1. Characteristics of infants by birthweight categories at UCSD ISCC

Specific Outcomes at UCSD ISCC, 1999

	<750	750-1000	1001-1500	>1500
Multiple birthweights (%)	14	33	28	6
Ventilated (%)	100	82	61	34
RDS (%)	91	86	55	6
Pneumothorax (%)	5	0	5	5
PDA (%)	41	54	36	7
NEC (%)	0	0	3	0
Sepsis >3 days any organism (%)	54	29	12	2
IVH >Grade 2 (%)	18	8	8	0

Characteristics and complications of infants by birthweight category at UCSD ISCC, 1999

n =	<750 22	750-1000 24	1001-1500 64	>1500 455
Inborn (%)	82	79	75	83
Outborn (%)	18	21	25	17
Survival (%)	82	83	97	97
CLD @ 36 weeks (%)	53	38	13	0
CLD (received steroids) (%)	36	30	3	0
ROP ≥ stage III (%)	14	0	0	0
Ventilation days (mean ± SD)	20 ± 20.3	9 ± 9.3	3 ± 3.3	6 ± 10.8

Characteristics and complications of infants by birthweight category at UCSD ISCC, 1998

n =	500 - 750 21	750-1000 29	1001-1500 44	>1500 471
Inborn (%)	76	79	78	80
Outborn (%)	24	21	22	20
Survival (%)	76	90	89	99
CLD @ 36 weeks (%)	85	33	5	0
CLD (received steroids) (%)	50	21	0	0
ROP ≥ stage III (%)	31	5	0	0
Ventilation days (mean ± SD)	23 ± 23.3	13 ± 22.9	4 ± 4.8	4 ± 5.2

Characteristics and complications of infants by birthweight category at UCSD ISCC, 1997

n =	500 - 750 20	750-1000 32	1001-1500 52	>1500 475
Inborn (%)	95	72	78	81
Outborn (%)	5	18	22	19
Survivors (%)	70	94	90	97
CLD @ 36 weeks (%)	69	35	19	0
CLD (received steroids) (%)	35	25	2	0
ROP ≥ stage III (%)	16	8	0	0
Ventilation days (mean & SD)	23 ± 34.2	8 ± 11.7	3 ± 4.1	3 ± 4.1

Table 2. Characteristics of infants by birthweight categories at SMBHW NICU

Specific Outcomes at SMBHW NICU, 1999

	<750	750-1000	1001-1500	>1500
RDS (%)	58	81	62	7
Pneumothorax (%)	5	0	4	<1
PDA (%)	42	53	51	2
NEC (%)	3	11	2	0
Sepsis >3 days any organism (%)	11	11	1	1
IVH > Grade 2 (%)	13	8	1	1

Characteristics and complications of infants by birthweight category at SMBHW NICU, 1999

	<750	750-1000	1001-1500	>1500
n =	38	36	85	953
Inborn (%)	87	75	71	84
Outborn (%)	13	25	29	16
Survival (%)	84	94	95	99
CLD (%)	47	44	15	<1
ROP ≥ stage III (%)	21	10	2	0
Ventilation (%)	63	83	74	9

Characteristics and complications of infants by birthweight category at SMBHW NICU, 1998

	<750	750-1000	1001-1500	>1500
n =	24	42	77	1059
Inborn (%)	92	90	86	93
Outborn (%)	8	10	14	7
Survival (%)	67	88	97	99
CLD (%)	33	19	8	0
ROP ≥ stage III (%)	21	11	1	0
Ventilation (%)	88	90	95	21

Characteristics and complications of infants by birthweight category at SMBHW NICU, 1997

	<750	750-1000	1001-1500	>1500
n =	14	40	67	682
Inborn (%)	93	78	90	91
Outborn (%)	7	22	10	9
Survival (%)	64	90	94	99
CLD (%)	29	25	16	<1
ROP ≥ stage III (%)	7	3	1	0
Ventilation (%)	100	88	76	30

bedside ultrasonographic evaluations, with hard-copy capability and formal report writing. The Fetal Assessment Unit (200 square feet) has a state-of-the-art Siemens Elegra ultrasound machine, fetal heart rate monitoring equipment and computer link-up which provides documentation and archiving of ultrasound examinations. Invasive fetal procedures can be performed in the Fetal Assessment Unit or the delivery room/operating room. Amniotic fluid testing is performed by a contracted laboratory and available within 3 hours of submission with a rapid amniotic fluid pulmonary maturity available within one hour. A full hospital laboratory is maintained 24 hours a day and is on the same floor with Labor and Delivery (L&D).

Obstetrical anesthesia expertise is overseen by Dr. Laurence Reisner, and provided by fellowship-trained obstetrical anesthesiologists, who provide a full-time obstetrical anesthesia service at UCSD. The ISCC is approximately 20 yards from the delivery area, with 40 approved beds, running at an average census of 30. Maternal and cord blood gas analysis is readily available from the ISCC.

The Fetal Diagnosis and Treatment Center of the Maternal Fetal Medicine is a California state-designated Prenatal Diagnostic Center (PDC). In the past year, over 3200 Level III consultative ultrasound examinations and greater than 1200 amniotic fluid karyotypic analyses were performed in the Center. Over 60% of all San Diego county referrals for the State of California mandated maternal serum screening program for neural tube and chromosome defects were performed by the UCSD Fetal Diagnosis Center. When the Sharp Perinatal volumes are added, the combined units evaluate more than 95% of all maternal serum screening cases in the San Diego County.

Twice monthly, a multidisciplinary conference is conducted by the Center. These unique conferences allow for detailed reviews and the development of plans for management of over 30 current high-risk pregnancies every two weeks. Dr. Kenneth-Lyons Jones, the Head of Dysmorphology at UCSD and the principal author of Smith's Recognizable Patterns of Human Malformation is a member of the Center, and also directs the California Teratogen Registry. The interaction of the Teratogen Registry, pediatric subspecialties including all pediatric surgical specialties, neurosurgery, urology, plastic surgery, general surgery, cardiovascular surgery and the prenatal diagnostic unit is continuously emphasized in patient management paradigms and conferences. In addition, Dr. Angela Scioscia, a Maternal Fetal Medicine specialist who is also a fully trained geneticist, appointed in both Obstetrics and Gynecology and the Department of Medicine, Division of Human Genetics at UCSD, directs the Fetal Diagnosis and Treatment Center and provides a unique expertise for fetal diagnosis.

The UCSD Perinatal Medicine group is currently involved in prospective studies to evaluate the role of Glyburide on glycemic control in diabetic mothers resistant to insulin, and is evaluating the glycemic index as a measure of diabetic control. Other current studies include a prospective evaluation of a dietary agent, acarbose, in reducing the need for insulin treatment of patients with gestational diabetes, a randomized trial of transdermal nitroglycerin for inhibition of preterm labor, and an investigation of fetal urinary flow rates using 3D ultrasound.

In-Patient Obstetrical Facilities: Sharp Mary Birch Hospital for Women (SMBHW): This facility, is one of only 10 stand-alone Women's Hospitals in the USA, and the only one west of the Mississippi. There are 22 Labor-Delivery suites and 8 dedicated obstetrical operating rooms. There is always 1 perinatologist, 2 obstetricians, and 2 obstetrical anesthesia specialists in house at SMBHW. All of these individuals are fellowship trained. Dr. Jack Schneider is the Medical Director of SMBHW, Women and Children's Services, and is a board-certified perinatologist. Dr. A. Pugh is Director of Obstetrical Anesthesia.

There are 2 ATL Ultramark-1000 ultrasound machines and an ATL Ultramark-IV ultrasound machine are kept in L&D for bedside ultrasonographic evaluations, and a new Sequoia ultrasound unit with hard-copy capability. The Fetal Assessment Unit (FAU) has an Acuson XP-128 ultrasound machine, fetal heart rate monitoring equipment and computer link-up which provides documentation and archiving of ultrasound examinations. Invasive fetal procedures can be performed in the FAU or the delivery room/operating rooms.

The NICU at SMBHW is located 2 floors below the delivery suites and operating rooms with 61 approved beds (31 level 3 and 30 level 1 and 2 beds), and has an average census of 40 to 45 occupied beds. Maternal blood gas analysis is readily available from the NICU. There are 2 dedicated resuscitation rooms adjacent to the L&D and Obstetrical OR's, and infants are stabilized in these areas before transport to the NICU using 2 dedicated high-speed elevators that enter directly into the NICU. This unique arrangement allows for excellent stabilization in an area that is fully equipped including monitors and neonatal ventilators, and then transport of the stable infant directly into the NICU by elevators that are always immediately available and an elevator ride of less than 30 seconds. Table 2 provides patient information from the SMBHW NICU for the past three years.

Perinatal Pathology: UCSD is fortunate to have Dr. Kurt Benirschke an Apgar Award winner and the foremost placental pathologist in this country, author of over 25 books including the textbook "Pathology of the Human Placenta"

as well as over 300 refereed publications. Dr. Benirschke attends the Fetal Diagnosis and Treatment Center conferences, organizes the weekly Perinatal Pathology Conference, and oversees the examination of all placentas and stillbirths and neonatal deaths. He has been involved in many of the observational studies conducted by members of the Maternal Fetal Medicine and Neonatology Divisions.

Perinatal Research Laboratories: Our Maternal Fetal Medicine division has a unique emphasis on maternal and fetal physiology and has large-animal laboratories that are specifically oriented to studying maternal and fetal physiology. There is an active basic research program under the direction of Dr. Brace and Dr. C. Cheung. They are involved in a number of studies on fetal physiology and the regulation of VEGF in their ovine fetal models. They have laboratories in the Surgical Research Building for housing pregnant sheep and conducting experiments on chronically catheterized fetal sheep. The facility occupies approximately 2,500 ft^2 and includes a surgical suite, a surgical preparation room, a necropsy and minor procedures room, and five large laboratories for performing acute as well as chronic experiments.

5. Facilities and Clinical Capabilities

Neonatology Clinical Facilities: The Neonatology Offices are located in the Multipurpose Faculty Building, which provides close proximity to the ISCC, the neonatology research laboratories, and to the Medical Center Library. As part of UCSD, we have complete access to the medical campus in La Jolla with support from the basic sciences as well as significant epidemiologic and biostatistical support. We are linked to the Medical Center and campus by computer, and our databases for patient information are maintained in this office area.

UCSD's Department of Laboratory Medicine has a wide range of laboratory tests available for hematology, chemistry, endocrinology, bacteriology, etc. We have access to sophisticated molecular methods for the diagnosis of bacterial and viral infections including PCR techniques for the diagnosis of infections including CMV and HIV.

Clinical Facilities UCSD Medical Center: The core NICU is a 40-bed regional neonatology unit that provides full support including cardiac surgery and ECMO with two complete ECMO carts. All beds have monitoring capability for heart rate, respiration, and pulse oximetry. Continuous monitoring of blood pressure is available at 20 bedsides, with dual or triple pressure monitoring at 8 bedsides. There are two dedicated blood gas analyzers (Chiron Model #865) equipped to perform basic electrolytes, glucose and lactate. There is a complete pulmonary function laboratory, three polygraphic recorders for sleep evaluations (Edentec II, Mallinckrodt), two dedicated flexible fibreoptic bronchoscopes (Olympus 2.2 mm and 3.5 mm with suction) and a dedicated video recording system to acquire images of all neonatal bronchoscopies. There are 19 Infant star ventilators, 18 of which are equipped with the recently updated high frequency module, and a Sensor Medics high frequency ventilator, two dedicated Ohmeda nitric oxide analyzers and delivery systems, as well as a chemiluminescence analyzer (Advanced Pollution Instrument, Model 200). The ISCC is connected through several unit servers to the hospital information system including medical records, laboratories, and in the near future, digital imaging will be available for immediate viewing of x-rays, ultrasounds and other diagnostic imaging procedures.

Systems are available to provide oxygen/air blended with heliox, nitrogen, or nitric oxide. There are 3 complete data acquisition systems (CODAS, Dataq, Columbus, OH), which are used to perform detailed long-term physiologic recordings of up to 16 channels of information.

The Division of Neonatology at UCSD is unique in having its own Department of Neonatal Respiratory Therapy, managed by Ellen Knodel, which is responsible to the Medical Director, Division Chief and Hospital CEO. This department has a staff of 16 full-time therapists skilled in all aspects of neonatal respiratory care with unique expertise in the areas of high frequency ventilation, continuous measurements of pulmonary mechanics, the performance of sleep studies including pH probes, the maintenance of the neonatology and pediatric bronchoscopes, and the provision of assistance during neonatal video-bronchoscopy. They are responsible for the acquisition and maintenance of all respiratory related equipment, including the blood gas analyzers, and Ms. Knodel has overall responsibilities for equipment evaluation and purchasing for the ISCC. The therapists perform all blood gas measurements, are able to draw blood from any indwelling line, and enter all patient related data for our unique respiratory database. This database contains information regarding all blood gases and associated ventilator parameters, including the use of CPAP, and allows the calculation of individual patient ventilator days. For teaching and quality assurance purposes this database contains information regarding housestaff procedures including intubations. All of the senior therapists are NRP certified, the majority as instructors, and all are competent at neonatal intubation. This group is also responsible for our ongoing quality assurance project involving the videotaping of all neonatal resuscitations performed in our main obstetrical operating room that involves the secure storage of the videotapes, loading the camera and initiating the videocapture, participating in the resuscitation, and removing the completed tape to be returned to the secure storage location. This group has been instrumental in our participation in a number of the previously described prospective

research projects, including the HIFI study, the human surfactant studies, and the prospective randomized trial of SIMV. A member of this group currently acts as a study coordinator for a number of ongoing multi-center studies, including the KL4 lavage study for hypoxic infants with meconium aspiration syndrome, the Curosurf comparative trial, and the hypothermia project. This individual will continue to assist Ellen Milan, our research nurse, with Network projects if we are successful in joining the NICHD Neonatal Network.

Neonatology offices are located in the Multipurpose Facility. There are 10 offices, four full-time and two casual support staff members, which includes an office manager, a financial office, and a data entry coordinator. The facilities include a library and conference room.

Sharp Mary Birch Hospital for Women Neonatal Unit: There is a 9,911 square-foot NICU that opened in November of 1992. It is divided into an acute care side with space for 31 ventilated babies and a step-down side for an additional 30 infants. The equipment is state of the art with each acute care bedside having monitoring capability for heart rate, 2 blood pressures, respiration, pulse oximetry, cardiorespirometry, and full 24 hour trending capability of all monitored parameters. All beds have fully integrated monitoring, charting and reporting functions via Clinicomp, EMR and IDX software that is also networked with the Obstetrical/Perinatal components of the EMR. Transcutaneous oxygen and carbon dioxide monitoring are available at each acute care bed. Fifteen dedicated neonatal respiratory therapists staff the Respiratory Department. There are two dedicated blood gas analyzers (Chiron Models #865) equipped to perform basic electrolytes, glucose and ionized calcium. In addition there are 2 Respiratory Therapists who are clinical specialists in charge of education and research. Each of them has greater than 15 years experience in pediatric and neonatology intensive care medicine. There are 13 Infant Star ventilators (several with high frequency capability), 5 Bird VIP ventilators, 3 Sensor Medics high frequency oscillators, 6 Servo 300A's, and 3 Infant Star Sync ventilators. There are 2 dedicated units for the administration of INO and a heliox delivery system.

There are 9 physician offices, a dedicated teaching conference room, a local neonatal computer network, including 11 personal computers with dual functionality for EMR and Sharp Healthcare intranet. In addition, SMBHW has a dedicated fully equipped, neonatal audio-visual computer laboratory under the direction of Dr G Bernstein. There are 3 administrative/secretarial support positions, a dedicated data acquisition analyst, and a program manager. SMBHW provides access to the Sharp Memorial Hospitals Medical Center Library and as part of the regional perinatal system, there is access to the UCSD Medical Library in La Jolla.

Neonatal Follow-up Program: The UCSD Infant Special Care Follow-Up (ISCFU) Program provides neurodevelopmental screening and case management for any high-risk infant discharged from the UCSD ISCC. The purpose of the ISCFU program is threefold: service, teaching and research.

Neurodevelopmental screening: Infants are enrolled in the ISCFU program just prior to ISCC discharge on the basis of neurodevelopmental risk. ISCFU staff performs a pre-discharge neurobehavioral assessment, with the parent present if possible. Follow-up appointments are scheduled at 4, 8, 12, 18, 24 and 36 (selected patients) months post-conceptual age. Each ISCFU visit includes an interim history, psychosocial assessment, anthropometrics, physical and neuromotor examination, and developmental assessment. Screening tools include the Amiel-Tison Neurologic Screen, Revised Knobloch-Gesell Developmental Screening Inventory and Early Language Milestone Scale. Patients are referred (or sub-contracted for specific research protocols) as needed to the Children's Hospital Developmental Evaluation Clinic for formal psychometry (e.g., Bayley Scale II, WISC-R) that is performed by experienced, infant/early childhood psychologists, at the Children's Hospital and Health Center of San Diego in their Developmental Evaluation Clinic. The ISCFU Program also provides consultation services with occupational and physical therapy, pediatric neurology, speech therapy and all other pediatric specialty services as required. The ISCFU clinic is not a primary care provider; and acute problems (e.g. otitis media, reactive airway disease) are treated and/or triaged as needed with referral back to the regular primary care provider.

Staff includes the physician director, Yvonne E. Vaucher, M.D., M.P.H., a full-time certified Pediatric Nurse Practitioner, and a full-time administrative assistant. The ISCFU clinic is integrated into the required Pediatric PL-I neurobehavioral rotation and into the Neonatology Fellowship Training Program. Neonatology fellows are required to spend a total of 128 hours directly involved in neurodevelopmental follow-up clinic activities. Clinic sites: Clinic is held at the central Ambulatory Care Center at UCSD Medical Center and at two community sites at the North and South County Public Health Centers. Records and database: Since 1989, all patient information, demographics, neuromotor exam and test results have been entered into an interactive database that is updated after every clinic visit. The database, which now contains information on over 3500 patients, can be queried very quickly and easily for any individual or group data desired. The ISCFU program maintains its own separate patient charts which contain relevant clinical information, consults, and reports, growth charts, neuromotor test results and all communications and authorizations

related to ISCFU visits. A comprehensive, typed report is sent to each child's primary care provider, service units and referral sources after every ISCFU clinic visit. This database is now being linked to all other neonatology databases. Patient demographics: Over the past five years, an average of 258 (range 235-289) new patients have been enrolled in the ISCFU program at the time of ISCC discharge. Approximately 450 (range 404-477) outpatient developmental assessments are performed every year. The ISCFU administrator is responsible for tracking all patients, speaking to all parents, scheduling all appointments and obtaining any necessary HMO or other authorization needed for the ISCFU visit. *Funding*: Approximately 60% of patients enrolled are MediCal (Medicaid) funded; 30% are contract (HMO) funded; and 10% are either cash pay or funded by private insurance. Approximately 15% of our patients are in foster care under Child Protective Services. *Race/ethnicity*: In 1999, 39% of our patients were non-Hispanic Caucasian; 47% had Hispanic surnames; 9% were African -American or East African; and 5% were Asian or Pacific Islander. *Language*: Approximately 15% of our patients' families speak only Spanish; for another 10% Spanish is the preferred language. The ISCFU nurse practitioner and administrative assistant are both sufficiently bilingual to schedule appointments and provide neurodevelopmental evaluation and services for the Spanish speaking families.

Follow-up rates: Compliance is approximately 60-65 % for all scheduled appointments, a rate that has been consistent for over 10 years. Follow-up compliance is most strongly influenced by whether or not funding is available for the visit. Whereas MediCal funds all neurodevelopmental follow-up visits; only 50 % of the contracted patients are authorized by their insurers for the ISCFU visit. The overall "show" rate by funding group is approximately 100% for foster care, 70% for MediCal, 50% for HMO, 10% for self-pay patients. Funded MediCal patients most often fail to return to the ISCFU clinic due to lack of transportation and family instability. Follow-up rates are also affected by the difficulties in tracking our highly mobile population. Our staff works closely with the Public Health nurses, Early Start, primary care providers, and California Protective Services to maintain ongoing contact with all enrolled families.

Follow-up rates for infants enrolled in prospectively identified research protocols are substantially better than the overall, unselected follow-up rates. Our follow-up for the HIFI Multicenter trial was 71%, one of the highest among US centers at that time. The multicenter TRH study follow-up rate was 85%. Our current experience for follow-up rate for current funded, prospective clinical trials is 85-90% (KL-4 and Head Cooling). Frequent contact by study personnel who establish an ongoing relationship with the family beginning in the ISCC before discharge has facilitated tracking and improved follow-up compliance. Based upon this experience, we anticipate that covering the cost of the neurodevelopmental evaluation, paying for transportation where needed and providing some incentive for the family, if possible, would result in a >85% compliance rate for study patients. Formal, standardized psychometry (e.g., Bayley Scales II, WISC-R, etc) is available as needed. The ISCFU program will be responsible for the follow-up of infants born at Sharp Mary Birch Hospital for Women who are enrolled in Network trials.

Research: The ISCFU program has long-standing experience participating in multicenter, prospective trials (i.e, human surfactant, HIFI, TRH, SIMV, KL-4, and Head Cooling). Since 1985, the ISCFU program has been the central component in multiple observational and retrospective case-controlled studies describing neurodevelopmental outcome in high risk infants including neonatal central nervous system injury [Grade III-IV intraventricular hemorrhage IVH, post-hemorrhagic hydrocephalus, white matter injury, ventricular dilatation, EEG abnormalities], congenital infection (syphilis), placental abnormalities (maternal floor infarction), multiple gestation (twin-twin transfusion, antenatal brain injury), maternal complications (prolonged, premature rupture of membranes), neonatal treatment (ECMO, CPR) and associated disease (CLD). The results of each of these studies have been briefly described in the previous sections on Academic Productivity.

In addition to the ISCFU program, Dr. Doris Trauner, Pediatric Neurologist at UCSD is a co-investigator in collaboration with the Center for Research in Language at UCSD, and is involved with 2 projects, the Origins of Communication Disorders (National Institute on Deafness & other Communication Disorders), and Neural Bases of Language & Learning (National Institute of Neurological Disorders & Stroke) directed by Dr. Elizabeth Bates. These studies evaluate language, behavior, intelligence, academic function and non-verbal communication (prosody), motor planning and spatial neglect in children after pre- or perinatal stroke and follow these children through adolescence. This research program currently follows infants in our program who have had a neonatal stroke, and in the near future, will also follow infants with periventricular leukomalacia (PVL). This group could provide expert consultation on aspects of evaluation of cognitive and language developmental in infants at risk from a variety of neonatal conditions and exposures. They currently utilize cognitive and language tests normed in Spanish, and all testing for Hispanic infants are administered by bilingual experienced staff.

Clinical Resources: The UCSD Medical Center has complete pediatric subspecialty consultative services available from 16 academic divisions. In addition, there are 2 full-time pediatric general surgeons, and pediatric surgical expertise is

available in all subspecialty areas including neurosurgery, urology, plastic surgery, ENT surgery, orthopedics, and cardiothoracic surgery (see List of Pediatric Subspecialties at the end of this document). All complex congenital cardiac conditions are treated at the UCSD Medical Center under the direction of the Division of Pediatric Cardiology, Dr. A Rothman, Division Chief, and Dr. Stuart Jamieson, Head of Cardiothoracic Surgery. There are 2 pediatric anesthesiologists who are trained and experienced in open-heart surgery, and a superbly trained and experienced group of perfusionists who also support neonatal and pediatric ECMO at UCSD. SMBHW has access to a full complement of medical and surgical pediatric consultants from CHHC and UCSD. Infants requiring complex surgery are transferred to CHHC from SMBHW.

6. Research Nurse Staffing

Ellen Milan, RN: Ms. Ellen Milan will be the research nurse for UCSD's participation in the Neonatal Research Network. Ms. Milan has been a neonatology nurse since 1972 and has worked in the nurseries at UCSD since 1978. She has been an administrative nurse, has advanced to the level of a Clinical Nurse IV and has also functioned as a neonatology nurse educator within our unit. She has actively participated in neonatal outreach programs and helped establish standards for the Infant Special Care Center. Ms. Milan was the research nurse responsible for UCSD's participation in the high-frequency oscillatory ventilation trial. In that study, she conducted in-services regarding the protocol, was involved in the randomization of eligible patients and performed the data collection as per the National Institutes of Health and Research Triangle Institute, maintained all records related to the infants enrolled and assisted with neurodevelopmental follow-up and pulmonary function testing. She was our research nurse for the safety and efficacy of filgrastim in the treatment of late onset neonatal sepsis, a study conducted by Amgen and, more recently, she was the research nurse for UCSD's involvement in the TRH and prevention of chronic lung disease trial. In that study, a local consortium was developed and Ms. Milan was able to coordinate activities among these three centers, including UCSD, the Balboa Naval Hospital and Kaiser Permanente. In all of these studies, Ms. Milan assisted with information provided to families, maintained and was responsible for completion of all case report forms and ensured that at all times, UCSD was compliant with the requirements of the study and completion of case report forms and notification of adverse events. Ms. Milan has been very active in outreach education, provided numerous neonatology outreach programs in California and, more recently, has been involved in the Project Concern International Romanian NEWSTART Program. She has lectured and run workshops in Sibiu, Romania in 1993, Timisoara in 1994, Riga, Latvia, Bucharest and a number of other centers in Romania in 1996, and will be teaching in Bucharest and Sighisoara in October 2000. Ms. Milan is a mature, experienced, highly competent and motivated nurse who has significant past experience in clinical research and is looking forward to her participation in the Network trials. In addition to Ms Milan, we have a number of nurses with previous clinical research experience, and a senior respiratory therapist who has is currently a site coordinator for three current clinical studies at UCSD and has worked with the pharmaceutical industry as a study coordinator. This individual will assist our research nurse and provide additional support for clinical trials. In addition, SMBHW has committed to hiring a full-time research nurse to facilitate their involvement in prospective multicenter randomized neonatology research (see Letters of Support from Ms. Henrikson, COO, SMBHW and Dr. Schneider, Medical Director, SMBHW). This individual will work in collaboration with and take direction from the UCSD research nurse, Ellen Milan, the SMBHW site Principal Investigator, Dr. Graham Bernstein, and the overall Principal Investigator, Dr. Neil Finer, for any Network project.

7. Unique Attributes

Diagnostic Imaging: We are able to perform a full range of the usual diagnostic evaluations including spiral, high speed and multi slice, CT scanning, and Magnetic Resonance imaging with a full complement of modalities including diffusion weighted imaging. UCSD has unique perinatal expertise in ultrasound imaging which includes 3- dimensional ultrasound under the direction of Dr. D. Pretorius, a pioneer in this field. Dr. Pretorius is a co-author of the Diagnostic Ultrasound and Fetal Anomalies - Text and Atlas Year Book Medical Publishers, 1990. Dr. Pretorius and Dr. T. Nelson continue to refine the use of 3-D ultrasound for obstetrical and neonatal applications.

Dr. G. Leopold, the Chairman of Radiology at UCSD, is himself a pioneer in the development of diagnostic ultrasound and author of "Fundamentals of Abdominal and Pelvic Ultrasonography" and "Ultrasonography of Pediatric Surgical Disorders."

Our Pediatric Neonatology Radiologists are Dr. S. Hilton, and Dr. D. Edwards, the author of over 65 articles and 11 book chapters. Together they are co-editors the textbook of Practical Pediatric Radiology, W.B. Saunders, 1994. Dr. Edwards has participated in a number of prospective clinical neonatal trials and performed independent radiological evaluations for such studies (Pediatr 1983;71:473-82, Chest 1983;83S:27-31, Chest 1983;83S:27-31, J Pediatr 1985;106:963-69, N Engl J Med 1986;315:785-90, J Pediatr 1991;118:581-94). Dr. Edwards is very willing to provide

independent consultative expertise, including blinded reading of films related to prospective trials conducted by the Network (see letter of support).

Pediatric Pharmacology Research Network (PPRU) and Pharmacokinetics: UCSD is of one of the original 7 NICHD PPRU sites with James Connor, M.D. (PI) and Edmund Capparelli, Pharm.D. (Co-PI), and we remain an active site in the PPRU program. The PPRU Network Program was created in 1993 by the NICHD with the mission to facilitate and promote pediatric labeling of new drugs or drugs already on the market. Each PPRU has experienced infrastructure to conduct clinical trials and laboratory facilities to develop and perform necessary pharmacologic assays. With the recent passage of FDA Modernization Act (FDAMA) and its provision for additional drug exclusivity for performing clinical studies in children, there has been a dramatic increase in industry interest in pediatric clinical trials. To help accommodate this increased demand, the NICHD expanded the PPRU Network to 13 sites in 1999. The PPRU has collaborated with other networks including the Collaborative Antivirals Study Group (CASG), Cystic Fibrosis Foundation Network and Research Units for Pediatric Psychopharmacology (RUPP) Network.

The UCSD PPRU has been integral to the development and successes of the overall PPRU Network function. In 1999 UCSD PPRU was one of the top two enrolling centers in the network participating in 27 of the 54 Network trials and serving as lead site in 9 of these studies. The UCSD PPRU is recognized within the PPRU Network as unique for its expertise on the use of sparse data collection and population methods to delineate important developmental pharmacokinetic and pharmacodynamic changes during infancy and childhood. Dr. E. Capparelli has represented the PPRU Network as a lecturer and consultant to the FDA on population pharmacokinetic study design and analysis in pediatric populations. In addition, Drs. J. Connor and E. Capparelli have been instrumental in the wide spread application of the population approaches to pharmacological studies performed within the Pediatric AIDS Clinical Study Group (PACTG). This includes a recently completed real-time population pharmacokinetic study of zidovudine in preterm infants that determined the metabolism and dosing requirements in this population.

There are clearly opportunities within current and future Neonatal Network studies to learn important and needed information regarding neonatal pharmacokinetics and pharmacodynamics with limited additional effort using sparse sampling and population pharmacokinetic analysis. As an example, little is known regarding the effects of prolonged hypothermia on neonatal drug metabolism, and the planned prospective hypothermia trial would provide a unique opportunity to evaluate the effects of hypothermia using sparse data collection. Midazolam, a drug that a significant number of these infants may receive, is metabolized by the cytochrome P450 3A family. This particular enzyme group is responsible for the oxidative metabolism of over half of all drugs that undergo phase I metabolism. With sparse pharmacokinetic sample collections obtained at key time points, a limited effort could generate important information regarding the development of metabolism of midazolam and effects of hypothermia. Since midazolam is considered a substrate probe for cytochrome P450 3A metabolic activity, this data would have had implications for many other important neonatal therapies.

The PPRU at our center provides expertise in the form of study coordinators, familiar with the requirements of regulatory agencies and is able to assist in completion of detailed case report forms. We believe that many of the network trials could provide needed and valuable information regarding drug metabolism, elimination and safety. We believe that a closer collaboration of the PPRU with the NICHD Neonatal Network will allow a much more rapid achievement of the overall goals of the PPRU and the FDA as these relate to the many orphan drugs currently utilized within the NICU. Our center in collaboration with our local PPRU and the PPRU network could provide coordination and centralization of sampling and analyses with real-time analysis (when necessary), in addition to significant statistical and pharmacokinetic analyses. Dr. N. Finer, the PI of this proposal, is a member of the newly formed Neonatal Drug Trials Task Force of the PPRU and is already working on the development of a prospective protocol to evaluate the efficacy and safety of ibuprofen for the management of PDA in premature infants. Dr. J. Connor, Director of the UCSD PPRU, is committed to support the participation of UCSD in the Neonatal Network and the potential further collaboration of the PPRU with the NICHD Neonatal Research Network (see Letters of Support).

Research Pharmacy: The Investigational Drug Service at UCSD Medical Center offers a number of unique services to assist investigators in conducting clinical research. The Investigational Drug Service will assist in executing the scientific, clinical and administrative aspects of approved clinical research. At the request of the investigator, the Investigational Drug Service can perform any or all of the following functions:

- Meet with study sponsor representatives to review study protocol and pharmacy procedures.
- Arrange for ordering and handling shipments of investigational drugs.
- Develop patient randomization schedules based on study protocols.
- Develop and/or provide compounding support for double blind studies.

- Set up procedures for accurate dispensing, record keeping and inventory control within the pharmacy.
- Provide Drug Information for medical, pharmacy and nursing staff. (Drug Information Fact Sheets).

Current operating protocols of the Investigational Drug Service indicate that drugs will only be dispensed by the Investigational Drug Service pursuant to a written chart order or prescription from the principal investigator or authorized co-investigators. Prior to the release of an investigational drug to a patient, the pharmacist will corroborate and document informed patient consent by requiring a copy of the current IRB approved, signed and dated consent form. Accurate and appropriate records as required by state and federal regulations, medical center policy, and the drug manufacturer will be maintained by pharmacy on all drugs dispensed. Inventory levels will be monitored and a running inventory will be maintained at all times. Upon termination of a study, copies of drug accountability will be stored for 20 years. Medications may be repackaged in single unit-dose containers or other containers that facilitate dispensing and administration when necessary. State and federal regulations as well as JCAHO and protocol guidelines for labeling will be observed. All investigational drugs will be properly stored to ensure stability and activity of the drug. Investigational drugs are stored and locked separate from commercially available medications within the Department of Pharmacy. Special procedures are in place to insure proper preparation of drug. Special compounding may be available at the request of the principal investigator.

All unused drug at the end of a study will be returned to the sponsor or properly destroyed, as requested by the study sponsor or principal investigator.

SMBHW also has an experienced investigational pharmacy offering similar services, and they are supportive of this application, and prepared to support relevant neonatal clinical drug trials (see Letters of Support).

UCSD Clinical Trials Office: This resource assists investigators with submissions to the IRB, adverse event reporting, monitoring forms and submitting IRB correspondence, and assists investigators with developing and submitting budgets.

UCSD General Clinical Research Center (GCRC): UCSD is the site of a NIH funded GCRC. This unit and its expertise are available to assist in any approved and sponsored clinical research activity. The GCRC can provide sophisticated sample collections, unusual tests (i.e., insulin/glucose levels, etc.) and other support services for infants in the ISCC at UCSD enrolled in IRB approved and sponsored trials using GCRC scatter beds (see Letters of Support).

Microbial Pathogenesis: UCSD has significant expertise and commitment in the areas of microbial pathogenesis, especially involving research on HIV and CMV, infections of great concern in neonatology. Thus Dr. Flossie Wong-Staal is the Florence Riford Chair in AIDS Research. With a grant from the National Institutes of Health, the Center for AIDS Research (CFAR) was established at UCSD in 1994 with Dr. Wong-Staal as its Director and Douglas Richman, M.D. as Co-Director. In 1996, the University of California Board of Regents approved the AIDS Research Institute, the equivalent of a department. The ARI, as it is known, encompasses the CFAR and is broadening and developing scientific collaborations with neighboring institutes, biotech companies, and expanding its public outreach and education program. Dr. Wong-Staal and her colleagues perform basic molecular studies focusing on the post-transcriptional regulation of retroviruses. In addition they are developing gene therapy against HIV using both an antiviral approach involving ribozymes targeting the HIV genome and cellular co-receptor genes, and an immune-based approach (transduction of dendritic cells) utilizing lentiviral vectors for gene delivery. Her laboratories are also developing a reverse functional genomic approach using randomized ribosome libraries to identify genes important for viral infections. Dr. Richman's laboratory focuses on the investigation of antiviral drugs and drug resistance, the interaction of HIV with different cell cells of the immune system, and the mechanism of lymphocyte killing by apoptosis, and HIV reservoirs and the pathogenesis of HIV-related disease during primary infection.

Dr. Deborah Spector, Professor of Biology is also involved in research relating to human CMV. Her focus is to determine at the molecular level how the interplay of viral and host functions relates to *in vivo* pathogenesis, and to use this information to develop effective strategies for treatment and prevention of disease. A major part of her research has focused on the regulation of human CMV early gene expression. In progress are studies utilizing both *in vivo* genetic analyses and *in vitro* biochemical assays to dissect the molecular regulation of these interactions. Her group is also studying the *in vivo* pathogenesis of cytomegalovirus, using murine cytomegalovirus (MCMV) as the model and attempting to develop a vaccine that will protect against not only morbidity and mortality, but also acute and latent infection.

Dr. Steven Spector, Vice Chair of the Department of Pediatrics, and Head of Pediatric Infectious Disease, is a recognized leader and authority in Pediatric HIV/AIDS, and herpes virology. He directs the Mother-Child-Adolescent HIV Program at UCSD. The Program is funded through the NIAID-sponsored Pediatric AIDS Clinical Trials Group (PACTG), and the Health and Human Services Ryan White Title IV Program. Studies of HIV-infected mothers and infants performed at UCSD through the PACTG have established the benefit of zidovudine in interrupting transmission

of HIV from mother to infant (PACTG 076), determined the pharmacokinetics of antiretrovirals in newborns, and identified the pharmacology and potential benefit of nevirapine administered late in pregnancy and shortly after birth to exposed infants. Additional studies have examined the immunologic response of HIV exposed infants to gp120 vaccines when administered shortly after birth. Dr. Spector is Chair of the Executive Committee of the PACTG that sets the national and international agenda for the group. Dr. Spector's laboratory examines the pathogenesis of HIV perinatal transmission. His research has identified important determinants of mother-to-infant transmission including maternal viral load, autologous neutralizing antibody, and viral phenotype. Current research is examining the impact of mother and infant chemokine receptor and chemokine genotypes on vertical transmission within the U.S. as well as in cohorts of mothers and infants in sub-Saharan Africa.

Dr. Wayne Dankner, an Associate Professor within the Division, has a particular interest in the pharmacokinetics of antiretrovirals in full-term and premature newborns. The Division participated in clinical trials that determined the efficacy of vidarabine and subsequently acyclovir in the treatment of neonatal herpes. More recently studies performed within the Antiviral Collaborative Study Group have examined the benefit of ganciclovir for the treatment of congenital CMV. Although preliminary, these results demonstrate that ganciclovir may be useful in decreasing hearing impairment in infants congenitally infected with CMV.

Dr. Sawyer has developed PCR assays for the detection of pathogens common in the neonatal period including herpes simplex, CMV, varicella zoster virus and enteroviruses. These assays are available through a rapid viral diagnosis laboratory directed by Dr. Sawyer. Dr. Victor Nizet, an Assistant Professor within the Division, examines the molecular pathogenesis of neonatal group B streptococcal (GBS) infection.

Thus, as can be seen, there is substantial expertise at UCSD as it relates to CMV, HIV, herpes, and GBS infections, four of the most serious and prevalent infections seen in newborn infants. In addition, UCSD has core laboratories in all related areas that would be available for performing cultures, assays, and related procedures should the Network become involved in research in these areas.

Biochemical Genetics: Dr. William L. Nyhan established the Division of Biochemical Genetics and Metabolism at UCSD in 1969. Dr. Nyhan's continuing efforts have made UCSD a world leader in the diagnosis and treatment of childhood metabolic disease. Dr. Bruce Barshop has joined Dr. Nyhan and has expanded the capability of their laboratory. This laboratory now offers 27 tests, not generally available, for the diagnosis of rare conditions. These tests include quantitative analyses of biotin, methylmalonic acid, a mitochondrial DNA panel, and southern blot, very long chain fatty acid measurements, MCAD common allele detection and fibroblast/amniocyte culture services.

This group would be able to provide centralized expert laboratory analyses for any relevant prospective studies planned by the Network.

The California Teratogen Information Service (CTIS): The California Teratogen Information Service (CTIS) is a statewide program operated by the Department of Pediatrics at the UCSD Medical Center under the direction of Dr. Ken Lyons Jones, Director of Dysmorphology. This service provides information about prescriptive and non-prescriptive drugs, street drugs, alcohol, chemicals, infectious diseases and any other physical agents that may be harmful to an unborn child. While a part of a nationwide community of Teratogen Information Services (TIS) known as the Organization of Teratology Information Services (OTIS), our program is one of only a very few that actively collects, collates and evaluates the information provided to determine the actual risks of pregnancy exposure on both fetal and neonatal outcomes [Chambers, C. D.; Anderson, P. O.; Thomas, R. G.; Dick, L. M.; Felix, R. J.; Johnson, K. A., and Jones, K. L. Weight gain in infants breastfed by mothers who take fluoxetine. Pediatr 1999 Nov; 104(5):e6].

Representation of Minorities and Adequate Gender Representation: Our patient population is unique with a very large proportion of ethnic Hispanic mothers and their children. In addition as can be seen from our payor mix, we provide care for a large indigent population. UCSD is also unique in that it has developed special programs for the recruitment of Women and minorities. The UCSD National Center of Leadership in Academic Medicine is a program funded by the Department of Health and Human Services as one of 4 programs created in 1998 by the U.S. Public Health Service's Office on Women's Health as a demonstration project to promote gender equity in medicine and leadership advancement of junior faculty. The principal investigator for this project is Dr. Vivian Resnick, a vice-chair of the Department of Pediatrics. The grant supporting this UCSD Center of Leadership establishes a formal coordinated program that provides mentoring, professional development and general support for 20 junior faculty (male and female) per year from the School of Medicine.

Dr. Vivian Resnick is also the academic coordinator of the Hispanic Center of Excellence (HCOE), (Principal Investigator: Dr. Sandra Daley, Department of Pediatrics). The HCOE was initiated in 1992 and has been refunded till 2003 by the Department of Health and Human Services, Public Health Service, Human Resources and Services

Administration, Bureau of Health Professions, with a mission to increase the number of underrepresented minority (URM) students and faculty at UCSD. This program supports academic enrichment at San Diego County schools, encourages and supports URM students to enroll in Medicine, and supports them during their medical education, and supports and conducts research and scholarly activities related to URM health and health care delivery issues. In addition, stipends are provided for 25 or more HCOE Scholars per year, as well as faculty release time for URM faculty to obtain further focused training. Between 1997-1999, the HCOE participated in recruiting and mentoring 18 new Hispanic professors.

8. Proposed Protocol Concept: "Early initiation of nasal CPAP (NCPAP) and expedited extubation followed by nasal SIMV (NSIMV) will decrease the duration of invasive mechanical ventilation and reduce the risk and severity of chronic lung disease in extremely low birthweight infants."

A. SPECIFIC AIMS:

1. To demonstrate that ELBW infants treated with early NCPAP, and, if criteria are met, a minimal period of intubation for surfactant administration followed by NSIMV post extubation, will require fewer total days of mechanical ventilation than infants given current conventional care without increasing mortality or the risk of IVH or PVL.
2. To demonstrate that compared with infants treated with conventional care, infants treated with early NCPAP and expedited extubation and followed by NSIMV will require fewer doses of surfactant; will have a lower risk of air leak; will have less CLD (oxygen requirement at 28 days, 36 weeks); will be exposed to less postnatal steroid use [decreased percent who receive, and decreased total dose, (mg/kg)]; will have fewer episodes of nosocomial sepsis; and will have a shorter length of stay and have no increase in neurodevelopmental sequelae at 18 to 24 months.

B. BACKGROUND AND SIGNIFICANCE

In spite of advances in ventilatory management, surfactant replacement therapies, and prenatal steroids, ELBW infants are still at high risk of developing CLD. Recent studies have reported that 92% of infants between 501-750 gm and 69% of infants of 751 to 1000 gm require oxygen at 28 days, and 60% and 39% require oxygen at 36 weeks post-conceptual age (PCA)[1,2,3,4]. The need for mechanical ventilation at 48 hours of age is the most important risk factor for the development of chronic lung disease (CLD)[5] and prolonged ventilation is a significant factor in the development of nosocomial sepsis, especially among infants with CLD[6]. Nosocomial sepsis accounts for up to 45% of late death, and significantly increases the length of stay by as much as 25 days[6]. Infants who develop CLD are more likely to require a longer duration of parenteral nutrition and have been shown to have less optimal growth[7]. Moreover, approximately 50% of ELBW infants in the USA currently receive postnatal steroids to prevent or treat CLD[3,8]. This treatment has been shown to substantially increase the risk of infection, and is associated with many other short term complications including poor growth, adrenal insufficiency, metabolic abnormalities, hypertension and bowel perforation and hemorrhage[9,10,11,12,13] and unacceptable long-term neurodevelopmental consequences[14,15,16].

The goal of the proposed research is to demonstrate that the duration of mechanical ventilation in ELBW infants can be reduced from that associated with the present standard of care through the early application of NSIMV and a protocol for early extubation, thus lowering the risk of CLD.

C. PRELIMINARY STUDIES/PROGRESS REPORT

The present approach to the ELBW infant is immediate intubation at birth with early surfactant replacement therapy, followed by mechanical ventilation, usually for substantial periods of time. Information from the VON Database indicates that approximately 90% of infants less than 1000 gm at birth require mechanical ventilation[3,17]. The current average duration of mechanical ventilation for ELBW infants in the US can be very prolonged[18]. Garland et al[19] and Sinkin et al[20] in studies of early postnatal dexamethasone, and Watterberg et al[21] using early postnatal hydrocortisone reported median durations of mechanical ventilation of 27 and 30 days, 20 and 27 days and 25 and 32 days for their treated and placebo groups, respectively.

Early extubation or the use of early continuous positive airway pressure (CPAP) may prevent much of the above morbidity in the ELBW infant. A survey of 8 neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD[22]. A more recent comparison of practices and outcomes between 2 neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993. This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used for 63% of infants at Columbia versus 11% at the Boston centers, and Columbia used less surfactant, 10% versus 45%, (all $p<0.001$)[23]. This study confirmed that the use of mechanical ventilation in the first week of life, and especially in the first 3 days (OR=13.4, CI 5.9, 30.7) was the highest risk factor for the development of CLD defined by oxygen dependency at 36 weeks PCA. There is now increasing

information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of ELBW infants. For infants who develop respiratory distress, intubation with surfactant treatment followed by expedited extubation may decrease CLD with no increase in other morbidities.

Jonsson et al, treated infants from 1988 to 1993 who required > 30% oxygen with nasal CPAP from soon after delivery. Infants were intubated for a PaCO2 greater than 60 mmHg with severe distress or apnea, and were given surfactant from 1991 onward[24]. Of all infants, 25% required only supplemental O2. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Only 24% of all infants received ventilation from birth. Almost all of their infants of ≤ 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al[25] from Bern Switzerland, reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality (p=0.038), and shortened the duration of intubation, and length of stay. Verder et al conducted the first prospective evaluation of early CPAP and short-term intubation for surfactant administration[26] in a Danish-Swedish multicenter collaborative trial conducted from Sept 1991 to October 1992. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). Verder et al performed a second multicenter prospective trial from April 1995 to Jan 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes[27]. This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days.

Lindner et al from Ulm, Germany recently reviewed their experience using a continuous prolonged (15 to 20 seconds) pressure controlled (20 to 25 cm H_2O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H_2O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation[28]. The criteria for subsequent intubation were a PaCO2 > 70 mmHg, an FiO2 >.6 and respiratory distress with severe recurrent apneas. They reported that the rate of early intubation and need for mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. All of the above studies required high levels of PaCO2 before initiating ventilation for this indication. Mariani et al recently reported that permissive hypercapnia in infants of 601 to 1250 gm reduced the median duration of ventilation from 9.5 to 2.5[29].

The use of non-invasive nasal ventilation at extubation may reduce the number of infants who require reintubation. We studied 54 infants < 1250 grams at planned extubation and randomized them to receive either nasal CPAP or nasal SIMV. The infants who received nasal SIMV had less extubation failures than the infants who received CPAP alone, 4/27 vs 12/27, p<0.05[30]. Similar results were reported by Friedlich et al[31] and Khalaf et al[32].

Reducing the overall length of intubation and the associated airway suctioning will also reduce the associated stress and the need for analgesia, which may effect later behavior and response to pain and analgesia[33,34,35,36]. In addition, the work of breathing is markedly increased with the use of the 2.5-mm endotracheal tube most often used for ELBW infants[37]. We believe that the use of less invasive ventilatory approaches will significantly reduce the risk of CLD, sepsis, decrease length of stay, without any increase in long-term neurodevelopmental sequelae, and should be more fully evaluated in the USA.

D. RESEARCH DESIGN AND METHODS

We propose to enroll approximately 540-700 ELBW infants in the Network for this study over 2 years (see sample size calculation). Infants will be randomized into those receiving conventional or experimental therapy prior to birth.

Inclusion Criteria: Infants of 500 to 1000 gm birthweight, who are AGA, inborn and without obvious malformations or chromosomal abnormalities for whom parental consent is obtained will be eligible.

Exclusion Criteria: Infants of less than 24 or greater than 30 completed weeks by certain LMP or early fetal ultrasound at < 20 weeks gestation will be excluded. Any infant with rupture of the membranes for > 2 weeks, and/or oligohydramnios of greater than 2 weeks duration, will be excluded.

I. Treatment for All Infants

1. All infants will have umbilical artery and vein catheters inserted where possible, and monitoring with TcPO2 (when feasible), TcPCO2 and SaO2 following admission to the NICU.
2. All infants will be given a loading dose of methylxanthine (aminophylline or caffeine) immediately after admission and stabilization in the NICU[38].
3. Postnatal steroids will be permitted in the first 72 hours of life only for the treatment of intractable hypotension using 1 mg/kg of hydrocortisone q 6-8 hours as needed to maintain the mean blood pressure appropriate for gestational age[39,40,41].

II. Infants randomized to *conventional* care will be treated as follows:

In the delivery room and the NICU, intubation, administration of surfactant, and use of nasal CPAP (NCPAP) or NSIMV may be provided at the attending physician's discretion and weaned according to current practice guidelines at each participating institution. (Individual institutional practice guidelines will be filed in advance for each study center).

III. Infants randomized to *experimental* treatment will be treated as follows:

Infants will be resuscitated in the delivery room as per usual management including intubation, surfactant administration or the use of mask or NCPAP at 5-6 cmH2O.

a. For infants intubated in the delivery room: After admission to the NICU, infants with birthweight **750 - 1000 gm** will be extubated to NSIMV within 2 hours of intubation, if they are stable, their arterial PaO2 is >50 mmHg on an FiO2 ≤ .35, their arterial PaCO2 is < 65 mmHg, and/or pH > 7.20 and they are not experiencing apnea requiring ventilation. For infants **< 750 gm** birthweight, the attempt at extubation will be made at ≥24 hours of age and after 7 am of the following morning if the above gas exchange criteria are met. Prior to planned extubation, infants will have nasal prongs inserted for the delivery of NSIMV and following extubation, will be ventilated synchronously via the nasal prongs at a rate of 20 breaths per minute (bpm), with effective pressures of 15/5, an inspiratory time of .4 seconds with an FiO2 sufficient to maintain an SaO2 > 90%. These pressures may be increased to a maximum of 20/5 and the rate of 30 bpm. Infants will be weaned to a rate of 4 – 6 NSIMV breaths over 48-72 hours, at which time the NSIMV will be discontinued, and the infant placed on NCPAP and then weaned as tolerated to nasal cannula or room air. The NSIMV may be continued beyond 48 - 72 hours at the discretion of the attending physician. NSIMV may be restarted for apnea, for a rising PaCO2, or for an increasing inspired oxygen requirement.

b. Intubation for surfactant administration at ≤ 72 hours for infants not intubated in the delivery room: These infants will remain on nasal CPAP at 5-6 cmH2O, and will be intubated and surfactant administered if they require an FiO2 > .35 to maintain an SaO2 > 90% or a PaO2 of ≥ 50 mmHg, or have a PaCO2 which has risen to > 65 mmHg and have a chest x-ray compatible with respiratory distress syndrome. These infants will be extubated to NSIMV and weaned according to the above procedures and guidelines in **IIIa**.

c. Intubation for apnea: Infants will be initially intubated or reintubated if they have apnea requiring bag and mask ventilation on more than 1 occasion in 12 hours, or a single episode requiring greater than 2 minutes of manual ventilation. Other criteria include the same gas exchange criteria for initial intubation (as described above), or the decision of the attending clinician that intubation is required (the reasons for which must be written on the case report form). Extubation to NSIMV will occur when these problems are resolved.

STATISTICS AND SAMPLE SIZE CALCULATIONS

We hypothesize that the early intubation group will have a significantly shorter total duration of ventilation. We postulate that we will reduce the duration of ventilation from a mean of 20 days for the control group to 12 days, (standard deviation = 20.3 days) for infants from 500 to 749 grams, and from a mean of 9 days to 5 days for infants of 750 to 1000 gm (standard deviation of 9.3 days), for reductions of approximately 40-44%. The control durations and standard deviations are derived from our 1999 database (See Table 1).

Projected Treatment vs Control Difference

Duration of Ventilation	20 days vs 12 days (500-749 gm)	9 days vs 5 days (750-1000 gm)
Number/Group, Power (CI,d)	110, 80%, (2.6, 13.4)	90, 80%, (1.3, 6.7)
Number/Group, Power (CI,d)	140, 90%, (3.2, 12.8)	120, 90%, (1.6, 6.4)

We estimate that we could enroll approximately 11-12 infants a year at UCSD and 19-20 infants at SMBHW for infants of 500-749 gm and 12-13 infants per year at UCSD and 17-18 infants from SMBHW from 750-1000 gm based on our 1999 statistics. Over a two-year study we would be able to enroll 118 to 126 infants at both sites. These numbers are based on 80% of inborn deliveries being available for prenatal or intrapartum consent, with a 20% refusal of such consent. We previously enrolled 54 infants < 1250 gm into our SIMV study over 2 years at UCSD alone[30] demonstrating our ability to enroll significant numbers of eligible patients from our nursery. This study would require

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between 400-500 eligible infants of 500 to 749 grams using a power of 80% to 90%, and estimating a mortality of 70% for infants of <750 gm. Thus for a power of 90%, if the parents of 500 eligible infants were approached for consent, and 80% consented, 400 infants would be randomized, and 70% would survive, resulting in 280 informative infants (140 per treatment group). In the group of infants from 750 to 1000 gm, similar calculations using a mortality of 80% would require 280 to 375 eligible infants for a power of 80% to 90%. For a network study, it would be assumed that such calculations would be based on actual values for birthweight specific length of ventilation and the associated standard deviation, and the current birthweight specific mortality from the Neonatal Network database, which could significantly alter the numbers required. We believe that from our knowledge of the Network, that there are more than enough infants from the representative units to complete such a study within a 2-year time period.

Statistical Analyses: We will utilize the Kaplan-Meier survival analysis, stratified for birthweight, to compare the primary outcome e.g., time to successful extubation from mechanical ventilation. The Cox Proportional Hazards Model will be used to examine the influence of predictor variables on the primary outcome. Univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birthweight, gestational age, the receipt of antenatal steroids, gender, treatment group, severity of illness, center, etc.) upon secondary outcomes (i.e., need for intubation in the first week of life, number of surfactant doses, incidence of air leak, exposure to post-natal steroids, occurrence of sepsis or CLD, IVH, PVL, death, length of stay, MDI, PDI, and occurrence of cerebral palsy.

Shortcomings: This cannot be a blinded study. Differences between the experimental and study groups may be diminished because of treatment creep toward the experimental method[42]. However the study design is such that we doubt that most investigators will attempt extubation of the control infants in the same time frame as the experimental infants. The protocol allows for the early prophylactic use of surfactant in the DR or shortly after admission to the NICU, and will encourage surfactant use within 2 hours of life for infants with early evidence of respiratory distress. We have chosen to set a minimum period of 24 hours for extubation of infants of <750 gm based on the current experience that infants of 24 weeks are not able tolerate early extubation, and that most American centers would find such early extubation in these infants unacceptable. There may be concern that surfactant should be used for more liberal criteria, and this and other issues will require discussion with the Network participants. The characteristics of the sample on study entry will be influenced by institutional differences in patient demographics and perinatal care (e.g., race/ethnicity, administration of antenatal steroids, management of preterm labor) which may influence outcomes examined. We will prepare a video of the appropriate placement of the nasal prongs and the use of the ventilator for NSIMV, and are prepared to provide training sessions as needed. We will request the manufacturer to provide synchronized IMV ventilators to Network units without such devices.

E. HUMAN SUBJECTS

In accordance with the Federal Policy on the Protection of Human Subjects (DHHS Policy 45 CFR Part 46, FDA Policy 21 CFR Parts 50 and 56), the University of California, San Diego (UCSD) is responsible for the protection of the rights and welfare of human subjects of research conducted by, or under the supervision of, faculty, staff or students. Any project, which will be conducted at this medical center, will require full IRB approval. Consent forms for such research must meet the rigid standards set by our IRB and almost always require modification and simplification. In addition, versions of such consents in Spanish are developed as needed, and must also meet IRB standards. The IRB at SMBHW hospital has identical standards, and any Network project will be submitted to both IRBs for their approval

F. VERTEBRATE ANIMALS: N/A

G. LITERATURE CITED: See below.

H. CONSORTIUM/CONTRACTUAL ARRANGEMENTS:

UCSD and SMBHW have established a collaborative agreement whereby these two centers will participate as a single site in the Network under the direction of Dr. Neil Finer (see Letters of Support).

I. CONSULTANTS:

Thomas Moore, MD, UCSD, Chair, Department of Reproductive Medicine, Paul Wozniak, MD, Medical Director, Neonatal Services at SMBHW, Val Catanzarite, MD, PhD, Director, Perinatal Imaging, Sharp Perinatal Center, and Edmund Capparelli, Pharm.D., UCSD Department of Pharmacology, will be consultants on the Network (see biosketches).

9. Intent to Participate in the Neonatal Research Network: UCSD Medical Center, School of Medicine and Neonatal Program and the SMBHW have thoroughly reviewed the requirements for participation in the NICHD

Neonatal Network and agree to follow all Network policies and procedures that govern its operations including those that relate to publications. Moreover, we agree to accept the coordinating role of the Neonatal Research Network group and the participatory and cooperative nature of the group. We are committed to supporting Network protocols, including the enrollment of all eligible consenting patients in approved clinical trials. We also are committed to the cooperative development of new and innovative protocols that will decrease the mortality and short and long-term morbidity of both premature and full-term infants who require intensive care. We understand that the Neonatal Research Network will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

10. Departmental and Institutional Commitments: Our Department of Pediatrics, UCSD Medical Center, School of Medicine and SMBHW are committed to participating in the collaboration research conducted by the NICHD Neonatal Research Network. Letters of Support are provided from:

Cecelia Smith, D.O., Director, UCSD HealthCare
Sumiyo Katelic, Director, UCSD Medical Center Hospitals
Stanley Mendoza, M.D., Chair, UCSD Department of Pediatrics
Mary Henrikson, COO, Sharp Mary Birch Hospital for Women
Jack Schneider, M.D., Medical Director, Sharp Mary Birch Hospital for Women
David Bailey, M.D., Dean, UCSD School of Medicine

These letters clearly express the commitment of these institutions to provide support for the neonatology units of UCSD and SMBHW to participate in the NICHD Neonatal Research Network.

11. Acceptance of Budgetary Mechanism We have the commitment of the Senior Administrators of both UCSD and SMBHW who agree to cooperate with the policy of capitation of research costs for the protocol base budgets and these institutions agree to provide assistance in the management and distribution of research funds (see Letters of Support).

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UCSD Medical Center
HILLCREST

July 1, 2000

Neil N. Finer, M.D.
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Re: Letter of Support

Dear Dr. Finer:

I am very pleased to support the application of the Division of Neonatology to participate in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. The UCSD Medical Center and School of Medicine is very supportive of appropriate prospective, multi-center research.

I know that the Division of Newborn Medicine has a strong and continuing commitment to develop and participate in relevant multi-center clinical trials. I believe that the addition of the UCSD Division of Newborn Medicine to the Neonatal Research Network will significantly enhance its overall productivity.

The UCSD Medical Center will work in a cooperative fashion with other members of the Neonatal Research Network and the NICHD as required by this application.

Sincerely,

Cecelia Smith, D.O.
Medical Director

Office of the Medical Director UCSD Medical Center, University of California, San Diego
200 WEST ARBOR DRIVE, SAN DIEGO, CALIFORNIA 92103-8972 TEL: (619) 543-2699 FAX: (619) 543-3676

UCSD Medical Center

July 1, 2000

NEIL N. FINER, M.D.
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Re: Letter of Support

Dear Dr. Finer:

The University of California, San Diego Medical Center is very pleased to support the application of the Division of Neonatology to participate in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. The Medical Center is very supportive of the significant clinical research conducted by your Division and your continuing participation in prospective, multi-center clinical trials.

The UCSD Medical Center is uniquely equipped to support your involvement in a collaborative research network. We have an extremely active and meticulous Institutional Review Board, a research pharmacy completely dedicated to prospective clinical research projects, and a staff which remains committed to our participation in meaningful clinical research.

We at the UCSD Medical Center hope you are successful in your application to join the NICHD Neonatal Research Network. We will provide any needed administrative and managerial support required and will agree to abide by the rules of such an award.

Sincerely,

Sumiyo E Kasteic

SUMIYO E. KASTEIC
Director

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June 7, 2000

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Professor of Pediatrics
Director, Division of Newborn Medicine
UCSD Medical Center

Dear Neil:

I am very pleased to learn that you are applying for membership into the NICHD Neonatal Research Network. As you are well aware, UCSD is very supportive of collaborative research and our faculty participates in a number of such nationally funded research organizations. We have a very supportive infrastructure at the School of Medicine and the Medical Center, including our Institutional Review Board, the Clinical Trials Group, and our Research Pharmacy as well as a broad array of clinical and basic science expertise. We provide care for a very ethnically, culturally, and socioeconomically diverse population.

Your group has been very active in both single center and multicenter prospective trials, and your participation in the Vermont Oxford Network NIC/Q 2000 project has demonstrated the benefit of true benchmarking at the Medical Center. I believe that your group would add a significant measure of innovation, expertise and enthusiasm to the NICHD Neonatal Research Network. I am pleased to note the collaboration with Sharp Mary Birch Hospital, and their commitment to this project, and believe that the 2 centers will contribute a meaningful number of ethnically diverse patients to future Network studies.

I am very supportive of your application to join this prestigious network. The UCSD School of Medicine will provide any required administrative support, and agrees to abide by the rules of such an award. Please do not hesitate to contact me if I can be of any assistance to you in this project.

Very truly yours,

David N. Bailey, M.D.
Interim Vice Chancellor for Health Sciences
Dean, UCSD School of Medicine

Finer, Neil N.

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

GENERAL CLINICAL RESEARCH CENTER

UNIVERSITY OF CALIFORNIA, SAN DIEGO
UCSD MEDICAL CENTER
200 WEST ARBOR DRIVE, 8203
SAN DIEGO, CALIFORNIA 92103-8203
(619) 543-6180 FAX: (619) 543-5536

March 2, 2000

Dr. Neil Finer
Director, Neonatology
UCSD Department of Pediatrics
8774

RE: COOPERATIVE MULTICENTER NEONATAL RESEARCH NETWORK

Dear Dr. Finer:

I am pleased to provide a letter of support for your NIH application noted above.

The General Clinical Research Center (GCRC) at UC San Diego provides resources and facilities for the conduct of clinical research. Our discrete eight bed inpatient/outpatient unit at the Hillcrest Medical Center and our outpatient facility on the School of Medicine La Jolla campus are staffed by registered nurses and registered dietitians to assist principal investigators with their patient oriented research. Our GCRC also provides a Metabolic Kitchen, Core Laboratory for special assays, computer and biostatistical support.

Protocols approved by the UCSD Institutional Review Board and the GCRC Advisory Committee can be conducted with the support of our facilities and staff.

Please let me know if you need any additional information, and we look forward to supporting this important project.

Sincerely,

Michael Ziegler

Michael G. Ziegler, M.D.
Program Director

Finer, Neil N.

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO SANTA BARBARA · SANTA CRUZ

STANLEY A. MENDOZA, M.D.
PROFESSOR AND CHAIRMAN
DEPARTMENT OF PEDIATRICS
SCHOOL OF MEDICINE

UCSD MEDICAL CENTER
200 WEST ARBOR DRIVE
SAN DIEGO, CA 92103-8444
TELEPHONE: (619) 543-6933
FAX: (619) 543-5512

July 1, 2000

Neil N. Finer, M.D.
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Re: Letter of Support

Dear Dr. Finer:

The Department of Pediatrics at the University of California, San Diego Medical School and Medical Center enthusiastically supports the application of the Division of Neonatology to become a member of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.

Your Division continues to be extremely active in clinical research and multi-center clinical trials. In addition, I am aware that you have participated in and collaborated with the NICHD Neonatal Research Network in the past.

I believe the addition of UCSD to the NICHD will further enhance its ability to conduct relevant prospective clinical research, taking advantage of our culturally diverse population and talented faculty. The Department of Pediatrics through our business office and departmental business officer will assist in the fiscal administration of this project, and provide managerial support as required for this award. You have my complete support in this endeavor.

Sincerely,

Stanley Mendoza, M.D.
Professor and Chair of Pediatrics

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Thomas R. Moore, M.D.
Professor and Chairman
Department of Reproductive Medicine
UCSD School of Medicine

200 W. Arbor Drive
San Diego, CA 92103-8433
Tel: (619) 543-7900 Fax: (619) 543-3703
E-mail: trmoore@ucsd.edu

June 2, 2000

Neil Finer, M.D.
Director of Neonatology
Professor of Pediatrics
UCSD Medical Center

Dear Dr. Finer:

I am very pleased that you are applying for membership in the NICHD Neonatal Research Network. As you and I have frequently discussed, UCSD is in an ideal position to meaningfully contribute to this very productive Network. Your group has been committed to prospective multicenter clinical research, and as you know, I was the local PI along with Frank Mannino for the antenatal TRH trial. Our enrollment and follow-up of the infants in that trial was excellent, and I believe that we would have similar success with the Network trials.

Our Maternal-Fetal Medicine group is committed to supporting such research. I would like to develop further combined Maternal-Fetal-Neonatal projects, such as the current antenatal steroid trial for fetal congenital diaphragmatic hernia from the CHD registry, of which you were the original author. Our group and all of the obstetricians in our practice are enthusiastically in support of the research conducted in your unit, and of your involvement in the Vermont Oxford Network. Your involvement in the benchmarking projects from the NIC/Q 2000 is already having an impact in our approach to meaningful quality assurance.

I am also particularly pleased that you have developed a consortium arrangement with Sharp Mary Birch Hospital for Women. I have great respect for their Maternal-Fetal Medicine department under Dr. David Schrimmer, and our group has continued to work collaboratively with their perinatologists. As you know Dr. Larry Cousins provides us with excellent coverage, and I believe that this initiative will lead to further productive collaborations with the group at SMB. The 12,000 deliveries from the Sharp system represent about 28% of deliveries in the San Diego county area and, combined with our unique and very high risk obstetrical population, will provide a large and very culturally diversified population of premature and critically ill neonates as potential subjects for future Network trials.

Our department pledges support for your participation in the Neonatal Network, including identification of mothers whose infants may be eligible for enrollment in specific trials. We recognize the importance of providing information regarding such studies to such families, and the ability to obtain consent prior to delivery. Our current practice of requesting neonatal consultation for all high-risk and premature pregnancies using your newly devised forms with current risk estimates for mortality and neurodevelopmental outcomes, should allow early and meaningful interaction and maximize the enrollment of eligible infants in such trials.

I wish you every success in this application. Please do not hesitate to contact me if I can be of any assistance in this process.

Yours truly

Thomas R. Moore
Professor and Chairman
Department of Reproductive Medicine
Director, Division of Maternal-Fetal Medicine

UCSD Medical Center
HILLCREST

May 31, 2000

Neil Finer, MD
Chief, Division of Neonatology
UCSD Medical Center
200 West Arbor Drive
San Diego, CA, 92103-8774

Dear Dr. Finer,

I am writing in support of your application to the National Institute of Child Heath and Human Development (NICHD) to become a member of the NICHD Neonatal Research Network.

The Infant Special Care Center at the University of California, San Diego has a long, well established history of being supportive, cooperative and successful in participating in multicenter national research projects. This has included our involvement in the HIFI trial, the human surfactant trial, the g-CSF trial in septic premature infants, the KL_4 premature study, and the TRH trial. We are currently enrolling infants in the KL_4 for term infants with meconium aspiration, and the hypothermia study. In addition, our recent experience in the Vermont Oxford Network NIC/Q 2000 stimulated the entire staff to re-evaluate the foundations for a number of our practices, and provided additional tools to facilitate such a process.

Our institutional commitment to medical education, research and clinical service has never been greater. Our nursing staff firmly believes in the value of rigorous clinical research to assist us in developing the evidence basis for effective therapies for our fragile infants. As a nursing department, we also value the opportunity to have our nurses expand their professional skills and knowledge by participating in such activities.

Your application to join the prestigious and productive NICHD Neonatal Research Network has the full support of the nursing staff of the Infant Special Care Center at UCSD Medical Center. I hope you are successful in your application and my staff and I look forward to working with you on this project.

Sincerely,

Linda Levy

Linda Levy, RN, MSN
Director, Women and Children's Services

Women and Infant Services UCSD Healthcare, University of California, San Diego
200 WEST ARBOR DRIVE, SAN DIEGO, CALIFORNIA 92103-8690 TEL: (619) 543-3518 FAX: (619) 543-2454

UCSD Medical Center
HILLCREST

May 31, 2000

Neil Finer, MD FRCP
UCSD Medical Center
200 W. Arbor Drive
San Diego, California 92103

Dr Finer,

I am writing in support for your application to the NICHD Neonatal Research Network. It is my understanding that participation in this network would allow the Neonatal Intensive Care Unit at the University of San Diego Medical Center (UCSDMC) to increase its participation in clinical trials. The Investigational Drug Service would be interested in participating and supporting these trials.

As you are aware the Investigational Drug Service (IDS) at UCSD is a 24 hour, 7 day a week operation and is supported by the Department of Pharmacy. The IDS offers a series of services to assist investigators in conducting clinical research. These include assisting in executing the scientific, clinical and administrative functions of research, meeting with study sponsor representatives to review study protocol and pharmacy procedures, arrange for ordering and handling shipments of investigational drugs, development of patient randomization schedules based on study protocols, development and/or providing compounding support for double-blind studies, provide procedures for accurate dispensing, record keeping and inventory control within the pharmacy, and provide Drug Information Fact Sheets for medical, pharmacy and nursing staff.

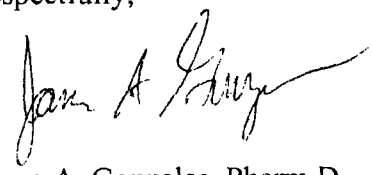
Prior to the end of this year, the IDS will provide protocol summaries and drug information fact sheets on investigational agents utilizing the intra-net system at UCSD. The IDS is financially supported by the School of Medicine, the Medical Center and by the Primary Investigators.

The Investigational Drug Service serves two hospitals at UCSD with a staff of 3.5 pharmacists and 1.0 FTE of technical support. Two of the pharmacists are voting members of the Institutional Review Board (IRB) for the School of Medicine. The IRB reviews over 1300 protocols per year. The IDS is responsible for approximately 250 trials per year. UCSD is currently is an active participant in many NIH supported clinical trial groups. These include: Cancer and Leukemia Group B (CALGB), Pediatric Oncology Group (POG), Gynecology Oncology Group (GOG), Aids Clinical Trials Group (ACTG), National Surgery Adjuvant Breast and Bowel Project (NSABP), and Radiation Treatment Oncology Group (RTOG).

In summary, the Investigational Drug Service is very excited about your participation in the NICHD Neonatal Research Network and look forward to a continued working relationship with you and your colleagues.

Pharmacy Administration *UCSD Healthcare, University of California San Diego*
200 WEST ARBOR DRIVE, ROOM 1317, SAN DIEGO, CALIFORNIA 92103-8765 TEL: (619) 543-6194 FAX: (619) 543-5829

Respectfully,



James A. Gonzales, Pharm.D.
Investigational Drug Service
Department of Pharmacy
UCSD Medical Center
Phone: (619) 543-2824
Fax: (619) 543-7698
e-mail: jagonzales@ucsd.edu

UNIVERSITY OF CALIFORNIA, SAN DIEGO

PEDIATRIC PHARMACOLOGY RESEARCH UNIT

of the

DEPARTMENT OF PEDIATRICS, UCSD

and

CHILDREN'S HOSPITAL OF SAN DIEGO

9500 Gilman Drive, M/C 0979
La Jolla, California, 92093-0979
Tel.: (858) 622-5729
Fax: (858) 622-9213
E-mail: jconnor@ucsd.edu

James D. Connor, M.D., Director
Edmund V. Capparelli, Pharm D., Co-Director
Angela Fornataro McMahill, J.D., Program & Contracts Manager
Jan Panyard-Davis, R.N., CCRC Clinical Nurse Coordinator
Rudy C. Torrez, L.V.N., Clinical Nurse Coordinator

June 1, 2000

Neil N. Finer, M.D.
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Re: Letter of Support

Dear Neil:

I am very interested in supporting your application for UCSD to become a participant in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.

As you know, the Pediatric Pharmacology Research Unit Network (PPRU) is very enthusiastic regarding opportunities to further evaluate the pharmacokinetics and pharmacodynamics of drugs in infants and the recent FDA Modernization Act has significantly increased interest and potential funding for such studies especially in newborn infants. The UCSD/CHHC PPRU in San Diego has been a member of the PPRU Network since its creation and is one of the most active sites in enrolling patients in PPRU Network studies.

Our PPRU has significant and unique expertise especially in the area of population pharmacokinetics. We believe that UCSD's membership in the Neonatal Research Network of the NICHD would provide significant new opportunities for evaluation of the neonatal pharmacokinetics and pharmacodynamics utilizing sparse sample sampling techniques and population pharmacokinetic analysis. In addition, the infrastructure of the PPRU provides significant expertise for participation in multicenter trials.

I am very hopeful that you will be successful in your application and that the NICHD Neonatal Network can have a closer working relationship with the PPRU Network. I think there is a tremendous potential for creative and productive synergy in this collaboration and the PPRU at UCSD is very supportive and will enthusiastically provide any assistance you require in your efforts to join and continue to participate in the NICHD Neonatal Network. I look forward to our ongoing collaboration and sincerely hope that you are successful in this endeavor.

Sincerely,

James D. Connor, M.D.
Department of Pediatrics
Professor and Chief, Section on Pharmacology
UCSD/CHHC Pediatric Pharmacology Research Unit (PPRU), and
PI UCSD Pediatric ACTG Pharmacology Laboratory

Departments of Radiology and Pediatrics
University of California Medical Center
200 West Arbor Drive
San Diego, CA 92103-8756
June 6, 2000

Neil Finer, M.D.
Director of Neonatology
Department of Pediatrics
University of California Medical Center
200 West Arbor Drive
San Diego, CA 92103-8774

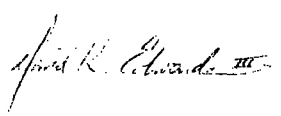
Dear Dr. Finer:

I am pleased, excited, and most supportive of your application to join the NICHD Neonatal Research Network. I am eager to participate in whatever ways I can with the research protocols developed in this regard, most particularly those that involve radiologic assessments of the patients and subjects.

As you know, I have experience in providing radiological evaluations of patients from multiple institutions as a part of multicenter trials. Should it prove desirable, I should also be glad to participate as an independent radiologic reviewer for network-wide studies.

Thank you for your efforts and attention.

With best regards,



David K. Edwards, III, M.D.
Professor of Radiology and Pediatrics

voice telephone: (619) 543-6657
FAX: (619) 543-3777
E-mail: de3@ucsd.edu

SHARP Mary Birch Hospital for Women

June 1, 2000

Neil Finer, M.D.
UCSD Medical Center
402 West Dickinson, Building MPF 1-140
San Diego, CA 92103

Dear Dr. Finer:

We write in support of Sharp Mary Birch Hospital for Women joining with UCSD Medical Center in application to the National Institute of Child Health and Human Development (NICHD) to become a member of the Neonatal Research Network.

As a licensed freestanding women's hospital, Sharp Mary Birch Hospital for Women has the largest delivery service and Neonatal Intensive Care Unit in California. The Regional Perinatal Program at Sharp Mary Birch Hospital for Women provides a continuum of care model from preconceptional and infertility services through antenatal diagnosis, perinatal special care (high-risk pregnancy), labor & delivery, newborn care, neonatal intensive care, discharge and followup care. Our staff has an over 10-year history of working as a multidisciplinary and interdisciplinary team. We not only work extremely well internally but also with outside agencies including UCSD Medical Center.

We are excited by the opportunity to become a partner with UCSD in this application. You are recognized as the principal investigator of this Sharp Mary Birch/UCSD research group. All applicable rules will be adhered to and required administrative support provided. Sharp HealthCare's Institutional Review Board is comprised of very experienced professional members. A full-time research nurse for Neonatal Medicine will be a member of our team by Fall.

As a partner in this collaboration, Sharp will offer significant advantages to the NICHD project. In addition to the large-sized service components, we offer a large, culturally diverse and very committed staff experienced in clinical research. This staff includes physicians, geneticists, nurses, therapists, pharmacists, laboratory specialists and administrators/directors.

The collaboration with UCSD and the NICHD is viewed with expectation and excitement. We intend to be a energetic and productive member of this consortium.

If you have any questions, please do not hesitate to contact either of us.

Sincerely,

Mary L. Henrikson
COO, SMBHW

Jack M. Schneider, M.D.
Medical Director, SMBHW

JMS:shs

(858) 541-4900 3003 Health Center Drive San Diego, California 92123

SHARP
MARY BIRCH
HOSPITAL FOR WOMEN

June 5, 2000

Dr. Neil Finer
UCSD Medical Center
402 West Dickinson, Building MPF 1-140
San Diego, CA 92103

Dear Dr. Finer,

As per our multiple conversations and discussions with the Neonatology Division at Sharp Mary Birch Hospital for Women, on their behalf I want to assure you we are excited and committed to the joint collaboration between Sharp Mary Birch Hospital for Women and UCSD to become a member of the NICHD Neonatal Research Network.

We have the support of the Administration, Nursing, Physicians and Ancillary Care. As you well know, we have a very long history of working collaboratively with our obstetricians and perinatologists. We have been successful in initiating and completing studies. When required by the studies, we have successfully obtained follow-up visits and data as requested.

Our research expertise is solid and expanding. If we are successful and become a part of the NICHD Neonatal Research Network, we will allot even more time to Dr. Graham Bernstein and myself to fulfill the research and administrative duties to assure the success of this program.

The N.I.C.U. statistics and numbers are included in the application. We compare very favorably to other units based on the Vermont Oxford Network Data. We are considered a site of excellence regarding infection control in that network

We are a full-service Women's Center and a full service NICU, and have an enthusiastic, competent, organized group of physicians who collaborate well not only with UCSD but with multiple outside agencies. We are eager to participate in the NICHD Network trials and welcome your leadership in this initiative. We believe that the collaboration between UCSD and Sharp will result in a very productive and efficient center for the NICHD Neonatal Research Network.

If you have any questions, please do not hesitate to contact me at 858-541-4170.

Sincerely,

Paul R. Wozniak, M.D.
Medical Director, Neonatal Medicine

SHARP
HEALTHCARE

June 2, 2000

Paul Wozniak, M.D.
Sharp Mary Birch Hospital for Women and Children
2929 Health Center Drive
San Diego, CA 92123

Dear Drs Wozniak and Finer,

I am writing in regards to your query concerning pharmacy support for clinical trials in the neonatal and pediatric population. Three years ago, Sharp HealthCare created a specialist position in pharmacy to coordinate the growing number of clinical trials in the system. I was hired for that position. Prior to that, I was the investigational drug pharmacist at the University of California at San Diego Medical Center.

My current responsibilities include the systemwide coordination of clinical research protocols using investigational drugs. This includes the development of pharmacy procedures for handling test articles, maintenance of study records in compliance with all regulatory agencies and staff education. The pharmacy has participated in the neonatal surfactant trials, and the ACTG antiviral trials at Mary Birch Hospital. You can be assured of continued pharmacy support for any new research studies in the future.

Attached is my curriculum vitae, which outlines my experience in pharmacy and clinical research. Please let me know how I may assist you and the neonatal group at Sharp HealthCare.

Sincerely,

Pauline J. Lew, Pharm.D.
Senior Specialist, Research Pharmacist
and Institutional Review Board Administration
Sharp HealthCare, Systemwide

Department of Pharmacy, Sharp Memorial Hospital 7901 Frost St San Diego, CA 92123 phone (858) 541-3717 fax (858) 541-6906

SHARP.

July 6, 2000

MARY BIRCH HOSPITAL FOR WOMEN

SHARP PERINATAL CENTER

Neil Finer, M.D.
University of California, San Diego
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Dear Dr. Finer:

I am very pleased that Sharp Mary Birch Hospital Women (SMBHW) will be collaborating with UCSD Medical Center in your application for membership in the NICHD Neonatal Research Network. SMBHW has a very active Maternal Fetal Medicine (MFM) Program and an excellent long standing working relationship with our neonatology colleagues. Our MFM Program has had a continuing commitment to perinatal research and has always had an excellent relationship with the UCSD MFM Program and Dr. Tom Moore.

The members of the MFM group are committed to supporting the participation of the SMBHW Neonatal Unit in the NICHD Neonatal Research Network. Our current practice of obtaining neonatal consultation for all of our high-risk deliveries will facilitate the identification of families whose infants may be candidates for specific trials. This process will allow for obtaining consent for relevant trials where it is needed before delivery and hopefully maximize our ability to enroll patients in relevant trials.

On behalf of my colleagues, I am happy to provide our commitment to support the activity of the SMBWH NICU as a participant with UCSD in the NICHD Neonatal Research Network and am pleased to act as a consultant for the MFM Program at SMBWH.

I hope you are successful in this application and look forward to working with you in the future.

Sincerely,

V Catanzarite

Val Catanzarite, M.D., Ph.D.
Director, Perinatal Imaging Sharp Medical Center
Co-Director, Sharp Children's Prenatal Diagnostic Center
Associate Clinical Professor, Department of Reproductive Medicine, UCSD

UNIVERSITY OF CALIFORNIA, SAN DIEGO

PEDIATRIC PHARMACOLOGY RESEARCH UNIT

of the

DEPARTMENT OF PEDIATRICS, UCSD

and

CHILDREN'S HOSPITAL OF SAN DIEGO

James D. Connor, M.D., Director
Edmund V. Capparelli, Pharm D., Co-Director
Angela Fornataro McMahill, J.D., Program & Contracts Manager
Jan Panyard-Davis, R.N., CCRC Clinical Nurse Coordinator
Rudy C. Torrez, L.V.N., Clinical Nurse Coordinator

9500 Gilman Drive, M/C 0979
La Jolla, California, 92093-0979
Tel.: (858) 622-5729
Fax: (858) 622-9213
E-mail: jconnor@ucsd.edu

July 6, 2000

Neil N. Finer, M.D.
Division of Neonatology
200 W. Arbor Dr., 8774
San Diego, CA 92103-8774

Re: Letter of Support

Dear Dr. Finer:

I am very interested in supporting your application for UCSD to become a participant in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. The UCSD/CHHC Pediatric Pharmacology Research Unit (PPRU) in San Diego has been a member of the NICHD Sponsored PPRU Network since the Networks inception and is one of the most active sites in enrolling subjects into PPRU Network studies. The PPRU Network is very enthusiastic regarding opportunities to further evaluate the pharmacokinetics and pharmacodynamics of drugs in infants. As you know, it has developed a Neonatal Drug Tasks Force (which both you and I are members) specifically to design and conduct clinical pharmacology studies that will ultimately improve drug dosing in newborn infants.

In addition, my research both in the PPRU and Pediatric AIDS Clinical Trials Group (ACTG) has focused on the role and application of population methods (using the program NONMEM) for determining pharmacokinetics and pharmacodynamic of drugs in pediatric populations. Our laboratory has been leading the effort to expand this method's use within the both the PPRU and Pediatric ACTG Networks. This approach utilizes limited samples per subject and is particularly advantageous for the neonatal population. I believe that UCSD's membership in the Neonatal Research Network of the NICHD would provide remarkable opportunities for nesting important neonatal pharmacokinetic and pharmacodynamic questions into the NICHD Neonatal Network trials utilizing sparse sample sampling techniques and population pharmacokinetic analysis.

I am very hopeful that you will be successful in your application and that the NICHD Neonatal Network can have a closer working relationship with the PPRU Network. For neonatal therapy issues I can envision tremendous synergy in this collaboration. I am very supportive of your efforts and will enthusiastically provide any assistance you require in your efforts to join. I will also make myself available to provide expertise in population analysis methods to the NICHD Neonatal Network. I look forward to our ongoing collaboration and sincerely hope that you are successful in this endeavor.

Sincerely,

Edmund V. Capparelli, Pharm.D.
Department of Pediatrics and Pharmacy
Associate Clinical Professor
UCSD/CHHC Pediatric Pharmacology Research Unit (PPRU)

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

[X] NEW application. *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

[ ] COMPETING CONTINUATION of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl. only)*
[ ] No
[ ] Yes. If "Yes," [ ] Previously reported [ ] Not previously reported

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

[ ] FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS
The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

-Human Subjects; -Vertebrate Animals; -Debarment and Suspension; -Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; -Lobbying; -Delinquent Federal Debt; -Research Misconduct; -Civil Rights (Form HHS441 or HHS 690); -Handicapped Individuals (Form HHS 641 or HHS 690); -Sex Discrimination (Form HHS 639-A or HHS 690); -Age Discrimination (Form HHS 680 or HHS 690); -Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 20.)*
All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
N/A	N/A	N/A

3. INDIRECT COSTS
Indicate the applicant organization's most recent indirect cost rate estab- lished with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal Agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Costs Rates*, and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. Indirect costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Awards, and specialized grant applications.

[X] DHHS Agreement dated: 06/23/99 [ ] No Indirect Costs Requested.

[ ] DHHS Agreement being negotiated with _____ Regional Office

[ ] No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on indirect costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base: $ 131,952 x Rate applied 51.5, 52 % = F & A costs (1) $ 68,450

b. Entire proposed project period: Amount of base: $ 711,317 x Rate applied 51.5, 52 % = F & A costs (2) $ 369,719

(1) Add to total direct costs from form page 4 and enter new total on FACE PAGE, item 7b.
(2) Add to total direct costs from form page 5 and enter new total on FACE PAGE, item 8b.

*Check appropriate box(es):

[ ] Salary and wages base [X] Modified total direct cost base [ ] Other base *(Explain)*
[ ] Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.)*:

4. SMOKE-FREE WORKPLACE
Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?

[X] Yes [ ] No *(The response to this question has no impact on the review or funding of this application.)*

AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services

691666 JUN 11'20

* PI: **PHELPS, DALE**

Grant #: 1 U10 HD040521-01

Dual:

IRG: ZHD1 SRC(99)

Council: 01/2001

Received: 07/01/2000

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

1. TITLE OF PROJECT
Rochester Center - Multicenter Neonatal Research Network

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*
Number: HD-00-010 Title: Cooperative Multicenter Neonatal Research Network

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR New Investigator ☐ YES

3a. NAME *(Last, first, middle)*	3b. DEGREE(S)	3c. SOCIAL SECURITY NO. *Provide on Form Page KK*
Phelps, Dale L.	M.D.	

3d. POSITION TITLE
Professor of Pediatrics

3e. MAILING ADDRESS *(Street, city, state, zip code)*
University of Rochester
Department of Pediatrics
601 Elmwood Avenue
Rochester NY 14642

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Department of Pediatrics

3g. MAJOR SUBDIVISION
School of Medicine

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: (716) 275-2972
FAX: (716) 273-1010

E-MAIL ADDRESS:
dale_phelps@urmc.rochester.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or NA per RFA	4b. Assurance of compliance no.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	5b. Animal welfare assurance no.
☐ No ☒ Yes	IRB approval date { ☐ Full IRB or ☐ Expedited Review	M-1357 IRB#01	☒ No ☐ Yes		

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
04/01/01	03/31/06	$109,220	$174,206	$572,500	$913,138

9. APPLICANT ORGANIZATION
Name: University of Rochester
Address: Department of Pediatrics
601 Elmwood Avenue
Rochester NY 14642

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER 1160743209A1
DUNS NO. *(if available)* 041294109

Congressional District 28

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Donna Galloway
Title: Research Administrator
Address: 518 Hylan Building
Rochester NY 14627

Telephone (716) 275-4031
Fax (716) 275-9492
E-mail dgallowa@orpa.rochester.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Donna Galloway
Title: Research Administrator
Address: 518 Hylan Building
Rochester NY 14627

Telephone (716) 275-4031
Fax (716) 275-9492
E-mail dgallowa@orpa.rochester.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* Dale Phelps MD

DATE 6/30/2000

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)* Donna Galloway

DATE 7/7/00

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The University of Rochester proposes to participate in the NICHD Collaborative Neonatal Research Network. This Network was formed 15 years ago to develop reliable scientific evidence for best clinical practice. By combining the populations of many intensive units, sufficient sample sizes of adequate diversity are enrolled in a reasonable time frame. The Network also collects prospective observational data for pilot projects, calculating sample sizes, and identification of key issues for future studies. Efforts are coordinated with a parallel Maternal-Fetal Medicine Network, and success and productivity relies on the creativity, design skills, experience and dedicated work of the center principal investigators that make up the Steering Committees, and the dedicated research staff that conduct the trials and collect the data.

Dale L. Phelps brings a wealth of personal experience in designing and conducting neonatal multi-center randomized trials. In addition, the other 10 academic faculty have also been conducting multi-center randomized trials and basic research for 18+ years, while caring for the1200 NICU admissions annually. They work closely with the Maternal-Fetal Medicine Division as the Regional Perinatal Center with established maternal transport of known high risk pregnancies, ensuring a stable population for recruitment. The NICU Follow-up Program evaluates all NICU graduates meeting high risk criteria (~ 20%), plus all infants in research protocols. In addition, all NICU graduates (high risk or not) are tracked via mailed annual questionnaires to families and physicians through age 5 years. Over 93% follow up has been accomplished for enrolled research subjects in follow up studies to date.

The Children's Hospital at Strong Perinatal Center at the University of Rochester has a large diverse neonatal population, experienced investigative faculty, and an outstanding Medical Research Institute. This center will be an outstanding participating Network Center. Dale Phelps as the PI, will be a dedicated participant and contributor on the Steering Committee and working subcommittees.

PERFORMANCE SITE(S) (*organization, city, state*)

University of Rochester School of Medicine and Dentistry
Department of Pediatrics, Division of Neonatology
Strong Memorial Hospital
Rochester, New York 14642

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Dale L. Phelps, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Principal Investigator
Linda Reubens, RN	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Research Nurse Coordinator
Gary Myers, MD	University of Rochester Sch. Medicine Departments of Neurology and Pediatrics, Division of Neonatology	Director, Neonatal Follow Up Program
James Woods, MD	University of Rochester Sch. Medicine, Dept. of Obstetrics Chief, Division of Fetal-Maternal Medicine	Collaborator, in Fetal-Maternal Medicine
William Maniscalco, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept. Division Chief of Neonatology	Neonatologist
Robert Sinkin, MD	University of Rochester Sch. Medicine	Neonatologist

	Division of Neonatology, Pediatrics Dept. Medical Director, NICU	
Ronnie Guillet, MD, PhD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist
Robert Swantz, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept. Associate Medical Director, NICU	Neonatologist
Nirupama Laroia, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist
Carl D'Angio, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist
Gloria Pryhuber, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist
Patricia Chess, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist
Timothy Stevens, MD	University of Rochester Sch. Medicine Division of Neonatology, Pediatrics Dept.	Neonatologist

Type the name of the principal investigator/program director at the top of each printed page and each continuation page. (For type specifications, see instructions on page 6.)

RESEARCH GRANT

TABLE OF CONTENTS

Research Plan

*Type density and type size of the entire application must conform to limits provided in instructions on page 6.

Appendix (*Five collated sets. No page numbering necessary for Appendix.*) [X] Check if Appendix is included

Number of publications and manuscripts accepted or submitted for publication (*not to exceed 10*) _____

Other items (*list*):

One page summaries of Currently Ongoing Research Projects
Reprint: STOP-ROP manuscript (1)

DD Principal Investigator/Program Director *(Last, first, middle):* Phelps, Dale L.

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 04/01/01 THROUGH 03/31/06

PERSONNEL *(Applicant organization only)* NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Dale L. Phelps	Principal Investigator	#	%	NA*	16,120 ~~14,130~~	3,064 2,686	see sal cap budget 16,816
Linda Reubens	Research Nurse			$	49,378	13,628	63,006
Nancy Voloskon	Data Entry				10,077	2,781	12,858
Gary Myers	Follow-Up Director			NA	--	--	--
*salary subject to federal cap of $141,300							
see budget justification for additional personnel							
with no requested salary							
SUBTOTALS →					75,575 ~~73,585~~	19473 ~~19,095~~	92,680

CONSULTANT COSTS

None — 0

EQUIPMENT *(Itemize)*

None — 0

SUPPLIES *(Itemize by category)*

Printing, paper, office supplies, envelopes, copy charges, computer disks, file storage off-site, postage, software, express postage, pager($3,600), small office equipment ($900) — 4,500

TRAVEL
10 x $954 — 9,540

PATIENT CARE COSTS — INPATIENT
OUTPATIENT

ALTERATIONS AND RENOVATIONS *(Itemize by category)*
None — 0

OTHER EXPENSES *(Itemize by category)*

Long distance phone/fax ($400); patient expense reimbursement and incentives ($2,100) — 2,500

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD $109,220

CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS
FACILITIES AND ADMINISTRATION COSTS

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* → $109,220

= Months Dedicated to Project
% = Percentage of Effort
$ = Institutional Based Salary

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD *(from Form Page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits Applicant organization only*		92,680	94,956	97,299	99,714	102,201
CONSULTANT COSTS		0	0	0	0	0
EQUIPMENT		0	0	0	0	0
SUPPLIES		4,500	4,500	4,500	4,500	4,500
TRAVEL		9,540	9,826	10,121	10,425	10,738
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
OTHER EXPENSES		2,500	2,500	2,500	2,500	2,500
SUBTOTAL DIRECT COSTS						
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
	F&A					
TOTAL DIRECT COSTS		109,220	111,782	114,420	117,139	119,939

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT *(Item 8a, Face Page)* → $ 572,500

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Budget justification (see next page)

BUDGET JUSTIFICATION:

Personnel:

Dale L. Phelps, MD is the principal investigator (PI) who assumes responsibility for all aspects of the Center's participation in the Network, and will be an active member of the Network Steering Committee for the development and implementation of new protocols. She directly oversees the operation of the Center through her work with, and supervision of the Research Nurse Coordinator. Dr. Phelps will commit at least % effort to this proposal.

Linda Reubens, RN is the Research Nurse Coordinator who is responsible for overseeing the conduct of the Network clinical trials, and is responsible, under the supervision of the PI, for adherence to the Network protocols, collection of data, supervision of data transmission, data quality, and staff training. She will attend the group meetings to learn about new protocols, and participate in quality assurance efforts study wide. Her entire effort % will be directed to the Network protocols.

Nancy Voloshon will fulfill the role of Data Entry Clerk who is responsible for data entry and transmission, be it electronic or by mail, and to ensure a final check of the completeness of all data forms. She is under the supervision of the Research Nurse and PI, and performs other support services to ensure smooth operations of the research office. She will travel to group meetings if required by the Network. Her minimum commitment to the Center will be % effort. The remainder of her full time appointment will be as a clinical documentation clerk so that she is always aware of all new admissions and is intimately familiar with the NICU database.

Gary Myers, MD, is the Medical Director of the High Risk Follow up Clinic, and will be responsible through that Clinic for the follow up tracking and performance of evaluations of the Network enrolled infants. No direct salary is requested, however partial support of the clinic's efforts will be offset by the capitation for follow up.

James Woods, MD, Chief of the Division of Maternal-Fetal Medicine will serve as the Collaborator from Fetal Maternal Medicine to the Neonatal Research Network. He will assume responsibility for assuring cooperation with Network protocols.

Other personnel without salary support will be involved in the care of infants enrolled in the Research Network, and these individuals are described in detail in the body of the application. They include the Neonatology staff and additional Research nurses. Unless supported through capitation funds, none of them will spend more than 0.1-3% effort on Network Protocols, but they are an important part of our resources and environment.

a) Collaborating Neonatologists: All of the Neonatal Faculty participate in the extensive clinical research activities of our Division. We work together to ensure relatively uniform approaches to patient care so that major changes in care do not occur with rotations. Biosketchs are provided and a greater description of their training and work is in the body of the application.
   William Maniscalco, MD, Division Chief
   Robert Sinkin, MD, Medical Director of the NICU

% = Percentage of Effort

Robert Swantz, MD, Associate Medical Director of the NICU
Nirupama Laroia, MD, Medical Director, Rochester General Hospital
Ronnie Guillet, MD, PhD, Medical Director, Highland Hospital
Patricia Chess, MD
Gloria Pryhuber, MD
Carl D'Angio, MD
Timothy Stevens, MD

b) Other research nurses

Marcia Dodge, RN is a research nurse in the Division of Neonatology currently funded at % FTE effort through three PHS/NIH/NEI grants at overlapping times in the next 2 years. She will be available to increase her time in accordance to Network needs and funded through the capitation. Meggan O'Hare, RN, NNP is a neonatal nurse practitioner who is an active investigator and part of our Clinical Trials Group who has designed two randomized controlled trials and one observational study. Her first RCT is published and we are in the middle of her second RCT.

Supplies and Small Equipment:

Supply costs are those primarily needed for the day to day communication, record keeping and work on the protocols, including toner cartridges for printers and FAX, paper, subject file folders, envelops, copy charges, computer diskettes, remote storage fees for closed files, postage, software, and express postage. The research nurse will also carry a pager to ensure availability at all times. $3600

A series of one time pieces of small equipment are necessary to maintain the function of the research office due to the relatively short working life span of many of these items. These run an average of $900 per year and include over the five year span, a desk in the first year, a locking file cabinet in the second and fourth years as our files expand, a new computer monitor at an unpredictable time, a replacement/upgraded computer, new hard drive for the existing computer and a new printer.

Travel:

Ten trips to attend regular meetings of the Technical Group and Steering Committee assuming these meetings require one night's stay, and to occur during the work week. Advance purchase, but non-excursion air fare to Washington DC from Rochester ($ 684, provided by University travel office with University discount), one night hotel ($160, allowing for taxes and surcharges on $140 base), University of Rochester food allowance ($35/day for two days), and incidental travel costs (airport parking, taxi/metro, taxes: $40).

Total per person-trip ($ 684 + 160 + 70 + 40) = $ 954
Total for 10 trips: 10 x $ 954 = $ 9,540

Other Expenses:

Long distance phone charges and equipment service contracts ($400) are based on actual expenses involved in maintaining communication with families in our extended region to ensure follow up. This also includes calls and FAX to the Data Coordinating Center at Research Triangle and with the Network Center in

% = Percentage of Effort

Bethesda, although use of e-mail has greatly reduced the need for such calls and the estimated amount of charges has thus been reduced. Parking passes and other minor reimbursement for family costs to travel for return to follow up clinic, and small toys for patient incentives have proven critical in our high success rate of follow up in past studies. Even token amounts mean a great deal to these families. We also use these funds to provide taxi transport where there are no other alternatives. ($ 2100)

Budget for the Entire Proposed Project Period:

The salary and fringe, travel and "Other expenses" have been increased by 3% per year. Supplies and small equipment have not been indexed, per instructions in the RFA.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Dale L. Phelps	Professor of Pediatrics and Ophthalmology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Pomona College, Claremont, CA	----	1962-65	Zoology
Northwestern University Medical School, Chicago, IL	B.M.S.	1966	Medicine
Northwestern University Medical School, Chicago, IL	M.D.	1969	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE

1971-74 Neonatal Fellow with R. Leake, W. Oh, C. Barrett, UCLA School of Medicine Hospitals
1974-80 Assistant Professor of Pediatrics, UCLA School of Medicine, Los Angeles, CA
1980-84 Associate Professor of Pediatrics, UCLA School of Medicine, Los Angeles, CA
1984-89 Associate Professor of Pediatrics and Ophthalmology, University of Rochester, School of Medicine, Rochester, NY
1989-pres Professor of Pediatrics and Ophthalmology, University of Rochester, School of Medicine, Rochester, NY
1993-97 NIH: NICHHD, Member of Research Advisory Committee

PUBLICATIONS (out of 75 original refereed publications)

- Phelps DL, Rosenbaum A. The role of tocopherol in oxygen induced retinopathy: kitten model. Pediatrics 1977;59(supp): 988-1005.
- Phelps DL, Rosenbaum A. Effects of marginal hypoxemia on recovery from oxygen-induced retinopathy in the kitten model. Pediatrics 1984;73:1-10.
- Phelps DL, Rosenbaum AL, Isenberg S, Leake RD, Dorey F. Efficacy and Safety of Tocopherol for Preventing Retinopathy of Prematurity. A Randomized Controlled Double-Masked Trial. Pediatrics 1987;79:489-500.
- Phelps DL. Reduced severity of retinopathy in kittens recovered in 28% oxygen. Pediatr Res 24:106-109 1988.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: Preliminary Results. [Phelps DL Permanent Executive Committee]. Arch Ophthal 1988;106:471-479.
- Kendig JW, Notter RH, Cox C, Aschner JL, Benn S, Bernstein RA, Hendricks-Munoz K, Maniscalco WM, Metlay LA, Phelps DL, Sinkin RA, Woods BP, Shapiro DL. Surfactant replacement therapy at birth: Final analysis, of a clinical trial and comparisons with similar trials. Pediatrics 1988;82:756-762.
- Sinkin R, Cox C, Phelps DL. Predicting risk for bronchopulmonary dysplasia: selection criteria for clinical trials. Pediatrics 1990;86:728-736.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: One Year Outcome - Structure and Function. (Phelps--Executive Committee) Arch Ophthalmol 1990;108:1408-1416.

- Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, Tung B on behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group: Incidence and Early Course of Retinopathy of Prematurity. Ophthalmology, 1991; 98:1628-1640.
- Palmer EA, Hardy RJ, Davis BR, Stein JA, Mowery RL, Tung B, Phelps DL, Schaffer DB, Flynn JT, Phillips CL: on behalf of the Cryotherapy for retinopathy of prematurity cooperative group. Operational aspects of Early Termination of the Multicenter Trial of Cryotherapy for retinopathy of prematurity. Controlled Clinical Trials 1991;12:277-292.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of a Cryotherapy for Retinopathy of Prematurity: 3½-Year Outcome--Structure and Function. (DL Phelps on Executive and Editorial Committees). Arch Ophthalmol. 1993;111:339-344.
- Sanders RJ, Cox C, Phelps DL, Sinkin RA. Two doses of early IV dexamethasone for the prevention of BPD in babies with respiratory distress syndrome. Peds Res 1994;36:122-128.
- Wagner CL,KramerBM,Kendig JW,Brooks JG,Cox C,Wagner MT,Phelps DL.School-Age follow-up of a single-dose prophylactic surfactant cohort. J Dev Behav Pediatrics 1995;16:327-332.
- Donahue ML, Phelps DL, Watkins RH, LoMonaco MB, Flood DG, Horowitz S. Retinal vascular endothelial growth factor (VEGF) mRNA expression is altered in relation to neovascularization in oxygen induced retinopathy. Current Eye Research 1996;15:175-184.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity: Snellen visual acuity and structural outcome at 5½ years after randomization. (DL Phelps on Executive and Editorial Committees). Arch Ophthalmol 1996;114:417-424.
- Dobson V, Quinn GE, Abramov I, Hardy RJ, Tung B, Siatkowski RM, and Phelps DL. Color vision measured with Pseudoisochromatic plates at five-and-a-half years in eyes of children from the CRYO-ROP study. Invest Ophthalmol Vis Sci, 1996;37:2467-74.
- Saunders RA, Donahue ML, Christmann LM, Pakalnis AV, Tung B, Hardy RJ and Phelps DL. Racial variation in retinopathy of prematurity (ROP). Arch Ophthalmol, 1997;115-604-608.
- Hardy RJ, Palmer EA, Schaffer DB, Phelps DL, Davis BR, Cooper CJ, on behalf of the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Cooperative Group: Outcome-based management of retinopathy of prematurity (ROP).J Am Assoc Ped Ophthal Stras 1997;1:46-54
- Phelps DL, Watts JL. Early light reduction to prevent retinopathy of prematurity in very low birth weight infants. Neonatal Module: The Cochrane Database of Systematic Reviews, Available in The Cochrane Library; Oxford: Update Software; Issue 2, 1997. Updated quarterly.
- Phelps DL, Lakatos L, Watts JC. D-Penicillamine to prevent retinopathy of prematurity. Neonatal Module: Cochrane Database of Systematic Reviews. The Cochrane Collaboration; Oxford: Update Software; Issue 2, 1998.
- Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens, LJ, Risemberg H and Phelps DL. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatr 1998;101:1006-1012.
- Sinkin RA, Kramer BM, Merzbach JL, Myers GJ, Brooks JG, Palumbo DR, Cox C, Kendig JW, Phelps DL. School age follow-up of prophylactic versus rescue surfactant trial: pulmonary, neurodevelopmental and educational outcomes. Pediatrics, 1998;101(5). URL: http://www.pediatrics.org/cgi/content/full/101/5/e11.
- Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease patterns in neonates. Pediatrics 1999;103(4):759-765.
- Anderson CC, Phelps DL. Peripheral retinal ablation in premature infants with threshold retinopathy of prematurity. Neonatal Module: Cochrane Database of Systematic Reviews, The Cochrane Collaboration; Oxford: Update Software; Issue 3, 1999.
- STOP-ROP Multicenter Study Group, (Phelps DL principal investigator) Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a Randomized Controlled Trial. I: Primary Outcomes. Pediatrics 105:295-310, 2000.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Linda J. Reubens	Certified Clinical Research Coordinator

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Monroe Community College, Rochester, NY	AAS	1988	Info. Systems
State University College of Arts and Science, Geneseo, NY	BS	1983	Management
Niagara County Community College, Sanborn, NY	AAS	1980	Nursing

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1975 – 1981 Patient Accounts Manager, Grand Island Manor Nursing Home, Grand Island, NY
1981 – 1986 Critical Care Nurse, Neonatal Intensive Care Unit, University of Rochester, Rochester, NY
1986 – present Clinical Research Coordinator, Division of Neonatology, University of Rochester, Rochester, NY

Honors
Member National Honor Society
Member Delta Mu Delta Honor Society

Publications

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, Sinkin RA, Bartoletti A, Dweck HS, Horgan MJ, Risemberg H, Phelps DL, Shapiro DL. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks gestation. New Engl J Med 1991;324:865-871.

Spafford PS, Sinkin RA, Cox C, Reubens LJ, Powell KR. Prevention of central venous catheter-related coagulase-negative staphylococcal sepsis in neonates. J Peds 1994;125:259-63.

Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens LJ, Risemberg H, Phelps DL. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multi-center randomized trial. Pediatrics 1998;101:1006-1012.

Abstracts

Kendig JW, Reubens LJ, Cox C, Risemberg, H, Bartoletti A, Dweck HS, Notter RH, Shapiro DL. A multi-center randomized trial of pre-ventilatory versus post-ventilatory administration of surfactant. Pediatric Research April 1989;25:220A.

Kendig JW, Reubens LJ, Cox C, Risemberg H, Bartoletti A, Dweck HS, Notter RH, Shapiro DL. A multi-center randomized trial of pre-ventilatory versus post-ventilatory administration of surfactant. The Physiologist August 1989;32:227.

Kendig JW, Cox C, Maniscalco WM, Sinkin RA, Reubens LJ, Horgan MJ, Dweck HS, Phelps DL. Surfactant prophylaxis as immediate bollus (IB) versus post-ventilatory aliquots. Pediatric Research April 1996;39:221A.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Gary J. Myers	Clinical Professor

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Kansas	BA	1957	Zoology
University of Kansas School of Medicine	MD	1963	Medicine
Harvard, Children's Hospital Medical Center	Fellowships	1971	Pediatrics, Neurology, Neonatology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PREVIOUS EMPLOYMENT

1963-1964 Children's Hospital Medical Center, Boston (Intern in Pediatrics)
1964-1966 Children's Hospital, Boston City Hospital, Boston (Resident, Pediatrics)
1966-1967 Children's Hospita, Boston City Hospital, Boston (Resident, Neurology)
1967-1969 U.S. Army, Womack Army Hospital, Ft. Bragg, NC (1 year pediatrics, 1 year neurology)
1969-1971 Children's Hospital Medical Center, Boston (Resident, Neurology)
1971-1974 Monroe Community Hospital, Rochester, NY, Pediatric Neurology Chronic Care Unit (Director)
1971-1978 Assistant Professor of Pediatrics and Neurology, University of Rochester School of Medicine.y
1978-1980 Associate Professor of Pediatrics, UAB School of Medicine
1981-1989 Professor of Pediatrics, UAB School of Medicine
1982-1989 Professor, Department of Special Education, UAB School of Education
1985-1989 Professor of Neurology, University of Alabama at Birmingham (UAB) School of Medicine
1989-1990 Visiting Professor of Toxicology in the Environmental Health Sciences Center, University of Rochester School of Medicine and Dentistry
1990-Present Professor of Neurology and Pediatrics, University of Rochester, Rochester, New York
1999-Present Acting Chief, Division of Pediatric Neurology, University of Rochester, Rochester, New York

PUBLICATIONS

Marsh DO, Clarkson TW, Myers GJ, Davidson PW, Cox C, Cernichiari E, Tanner MA, Lednar W, Shamlaye C, Choisy O, Hoareau C, and Berlin M. The Seychelles Study of Fetal Methylmercury Exposure and Child Development: Introduction. Neurotox 16(4):583-596, 1995.

Shamlaye C, Marsh DO, Myers GJ, Cox C, Davidson PW, Choisy O, Cernichiari E, Choi A, Tanner MA, and Clarkson TW. The Seychelles Child Development Study on Neurodevelopmental Outcomes in Children Following in utero Exposure to Methylmercury from a Maternal Fish Diet: Background and Demographics. Neurotox 16(4): 597-612, 1995.

Cernichiari E, Toribara TY, Liang L, Marsh DO, Berlin M, Myers GJ, Cox C, Shamlaye CF, Choisy O, Davidson PW, and Clarkson TW. The Biological Monitoring of Mercury in the Seychelles Study. Neurotox 16(4): 613-628, 1995.

Myers GJ, Marsh DO, Cox C, Davidson PW, Shamlaye CF, Tanner MA, Choi A, Cernichiari E, Choisy O, and Clarkson, TW. A Pilot Neurodevelopmental Study of Seychellois Children Following in utero Exposure to Methylmercury from a Maternal Fish Diet. Neurotox 16(4): 629-638, 1995.

Myers, GJ, Davidson, PW, Cox, C, Shamlaye, CF, Tanner, MA, Choisy, O, Sloane-Reeves, J, Marsh, DO, Cernichiari E, Choi A, Berlin M, and Clarkson TW. Neurodevelopmental Outcomes of Seychellois Children sixty six months after in utero exposure to methylmercury from a maternal fish diet: Pilot study. Neurotox 16(4): 639-652, 1995.

Myers GJ, Marsh DO, Davidson PW, Cox C, Shamlaye CF, Tanner MA, Choi A, Cernichiari E, Choisy O, and Clarkson TW. Main neurodeveopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: Outcome at six months. Neurotox 16(4): 653-664, 1995.

Davidson PW, Myers GJ, Cox C, Shamlaye CF, Marsh DO, Tanner MA, Berlin M, Cernichiaria E, Sloane-Reeves J, Choisy O, Choi A, and Clarkson, TW. Neurodevelopmental Test Selection, Administration and Performance in the Main Seychelles Child Development Study. Neurotox 16(4): 665-676, 1995

Davidson PW, Myers,GJ, Cox C, Shamlaye C, Choisy O, Sloane-Reeves J, Cernichiari E, Marsh DO, Berlin M, Tanner MA, and Clarkson TW. Longitudinal Neurodevelop- mental Study of Seychellois Children Following *in utero* Exposure to Methylmercury from Maternal Fish Ingestion: Outcomes at 19 and 29 Months. Neurotox 16(4): 677-688, 1995.

Lapham LW, Cernichiari E, Cox C, Myers GJ, Baggs RB, Brewer R, Shamlaye CF, Davidson PW, and Clarkson TW. An Analysis of Autopsy Brain Tissue from Infants Prenatally Exposed to Methylmercury. Neurotox 16(4): 689-704, 1995.

Cernichiari E, Brewer R, Myers GJ, Marsh DO, Lapham LW, Cox C, Shamlaye CF, Berlin M, Davidson P, and Clarkson TW. Monitoring Methylmercury During Pregnancy: Maternal Hair Predicts Fetal Brain Exposure. Neurotox 16(4):705-710, 1995.

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Tanner MA, Marsh DO, Cernichiari E, Lapham LW, Berlin M, and Clarkson TW. Summary of the Seychelles Child Development Study on the Relationship of Fetal Methylmercury Exposure to Neurodevelopment. Neurotox 16(4): 711-716, 1995.

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Choisy O, Cernichiari E, Choi A, Sloane-Reeves J, Axtell C, Gao P, and Clarkson TW. The Seychelles child development study: results and new directions through twenty-nine months. Water, Air, Soil Pollut 97: 53-61, 1997.

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Tanner MA, Marsh DO, Cernichiari E, Lapham LW, Berlin M, and Clarkson TW. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles child development study. Neurotox 18:819-830, 1997.

Myers GJ, Davidson PW, Weitzman M, Lanphear B. The contribution of heavy metals to developmental disabilities in children. Mental Ret Devel Dis Res Reviews 3:239-245, 1997.

Davidson PW and Myers GJ. Overview: Environmental contaminants and developmental disabilities. Mental Ret Devel Dis Res Reviews 3: 221-222, 1997.

Myers GJ, Davidson PW, Shamlaye CF. A review of methylmercury and child development. Neurotox 19:313-328, 1998.

Myers GJ and Davidson PW. Low level prenatal methylmercury exposure and children: Neurological, developmental and behavioral research. Environ Health Perspect 106 (Supp 3): 841-849, 1998.

Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, Cernichiari E, Needham L, Choi A, Wang Y, Berlin M, Clarkson TW. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neuro-development: Outcomes at 66 months of age in the Seychelles child Development Study. JAMA 280(8): 701-707, 1998.

Axtell CD, Myers GJ, Davidson PW, Choi AL, Cernichiari E, Sloane-Reeves J, Shamlaye C, Cox C, Clarkson TW. Semiparametric modeling of age at achieving developmental milestones after prenatal exposure to methylmercury in the Seychelles Child Development Study. Environ Health Perspect 106: 559-564, 1998

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
James R. Woods, Jr., M.D.	Professor of OB-GYN, Director of Obstetrics & Maternal-Fetal Medicine, Associate Chair of OB-GYN

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Alleghany College, Meadville, NY	B.S.	1966	Pre-Medicine
Bowman College of Medicine, Winston-Salem, NC	M.D.	1970	Medicine
Tripler Army Medical Center, Honolulu, HI			
UCLA School of Medicine, Los Angeles, CA			

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1986 – present	Director of Obstetrics and Maternal-Fetal Medicine, University of Rochester School of Medicine and Dentistry
1991-present	Professor of Obstetrics and Gynecology
1993-present	Associate Chairman, Dept. of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry

PUBLICATIONS

Skillman CA, Plessinger MA, Woods JR, Clark KE: Effect of graded reductions in utero-placental blood flow on the fetal lamb. Am J Physiology (Heart Circ Physiol) 249:H1098-H1105, 1985.

Plessinger MA, Woods JR: Fetal auditory brainstem response: External and intrauterine auditory stimulation. Am J Physiol 250:R137-D141, 1986.

Woods JR, Plessinger MA: The fetal visual evoked potential. Ped Research 20:351, 1986.

Woods JR, Plessinger MA, Clarke KE: The effects of cocaine upon uterine blood flow and fetal oxygenation. JAMA 257:957-61, 1987.

Plessinger MA, Woods JR. Fetal auditory brainstem response: Effect of increasing stimulus rate during functional auditory development. Am J OB GYN 157:1382-87. 1987.

Woods JR, Plessinger MA, Scott K, and Miller RK: Prenatal cocaine exposure to the fetus: A sheep model for cardiovascular evaluation. Annal NY Acad Sci 562:267, 1989.

Woods JR, Plessinger MA. Fetal sensory sequencing: Applications of evoked potentials in perinatal physiology. Seminars in Perinatol 13:380-92, 1989.

Woods JR, Plessinger MA: Pregnancy increases cardiovascular toxicity to cocaine. Am J OB GYN 162:529-33, 1990.

Dolkart LA, Plessinger MA, Woods JR. Effect of alpha-1 receptor blockade upon maternal and fetal cardiovascular responses to cocaine. Obstet Gynecol 75:745-51, 1990.

Woods JR, Plessinger MA: Maternal-fetal cardiovascular system: A target of cocaine. NIDA Research Monograph 108:7-27, 1991.

Plessinger MA, Woods JR: The cardiovascular effects of cocaine use in pregnancy. Reprod Toxicol 5:99-113, 1991.

Plessinger MA, Woods JR: Progesterone increases cardiovascular toxicity to cocaine in nonpregnant ewes. Am J Obstet Gynecol 163:1659, 1990.

Thadani PV, Woods JR: Cardiovascular toxicity of cocaine: Underlying mechanisms. J Applied Cardiol 5:317-20, 1990.

Woods JR: Cardiovascular effects of cocaine in pregnancy and on the fetus. NIDA Research Monograph 119:111-15, 1992.

Sharma A, Plessinger MA, Sherer DM, Liang CS, Miller RK, Woods JR: Pregnancy enhances cardiotoxicity of cocaine: Role of progesterone. Toxicol & Applied Pharmacol 113:30-35, 1992.

Abramowicz JS, Sherer DM, Woods JR: Acute transient thrombocytopenia associated with cocaine abuse in pregnancy. Obstet Gynecol 78:499-503, 1991.

Sharma A, Plessinger MA, Miller RK, Woods JR: Progesterone antagonist mifepristone (RU486) decreases cardiotoxicity of cocaine. Proceedings of the Society for Experimental Biology and Medicine 202:279-87, 1993.

Glantz JC, Woods JR: Cocaine, heroin, and phencyclidine: Obstetrical perspectives. Clinical Obstetrics and Gynecology 36, 1993.

Plessinger MA and Woods JR: Maternal, placental, and fetal pathophysiology of cocaine exposure during pregnancy. Clin Obstet and Gynecol 36, 1993.

Rib D, Sherer DM, Woods JR: Maternal and neonatal outcome associated with prolonged premature rupture of membranes below twenty-six weeks gestation. Am J Perinatol 10:369-73, 1993.

Woods JR, Scott KJ. Plessinger MA: Pregnancy enhances cocaine's actions upon the heart and within the peripheral circulation. Am J OB GYN 170:1027-35, 1994.

Woods JR: Fourth Triennial Report to Congress. Maternal and fetal effects of in-utero drug exposure: Perinatal effects.

Mahone PR, Scott K, Sleggs G, D'Antoni T, Woods JR: Cocaine and metabolites in amniotic fluid may prolong fetal drug exposure. Am J OB GYN 171:465-69, 1994.

Woods JR. Clinical management of drug dependency in pregnancy. NIDA Research Monograph Series #149, 1995.

Woods JR: Clinical management of drug dependency in pregnancy. Scientific Review. NIDA, 1993.

Woods JR: Adverse consequences of prenatal illicit drug exposure. Current Opinion in Obstetrics and Gynecology 8:403-11, 1996.

Woods JR, Plessinger MA, Fantel A: An introduction to reactive oxygen species and their possible roles in substance abuse. Obstetrics and Gynecology Clinics of North America 25:219-36, 1998.

Plessinger MA and Woods JR. Cocaine in Pregnancy: Recent data on maternal and fetal risks. IN: Obstetrics and Gynecology Clinics of North America. Woods JR (Guest Editor). W. B. Saunders Co, p. 99-118, 1998.

Woods JR. Maternal and transplacental effects of cocaine. Annals of the New York Academy of Sciences 846:1-11, 1998.

Woods JR: Translating basic research into the clinical setting. National Institute on Drug Abuse - Drug Addiction Research and the Health of Women. Wetherington CL and Roman AB (eds). NIH Publication #98-4290, June 1998, pp. 187-195.

Plessinger MA, Woods JR, Miller RK. Pretreatment of human amnionchorion with vitamins C and E prevents hypochlorous acid-induced damage. *In Press*. Am J Obstet Gynecol 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Patricia R. Chess	Assistant Professor in Neonatology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Colgate University, Hamilton, NY	B.A.	1983	Chemistry/Mathematics
Columbia University, New York, NY	M.D.	1988	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1983-84	Faculty, Dept. of Chemistry, Colgate University, Hamilton, N.Y.
1983-84	Faculty Advisor-Colgate University, annual publication of student research
1984 summer	Research Assistant, Medical College of Ohio, Toledo, Ohio
1988-91	Pediatric Internship, Residency, Strong Memorial Hospital, Rochester, N.Y.
1991	Chief Resident, Outpatient De partment, Strong Memorial Hospital, Roch, N.Y.
1991-94	Fellowship in Neonatology, Strong Memorial Hospital, Rochester, N.Y.
1994-1996	Senior Instructor in Neonatology, Strong Memorial Hospital, Rochester, N.Y.
1996-present	Assistant Professor in Neonatology, Strong Memorial Hosp, U of Roch, N.Y.

HONORS AND AWARDS

1979	Valedictorian, Cardinal Mooney High School
1979-83	New York State Regents Scholar
1983	Cum Laude, Honors in Chemistry, Colgate University
1984	Stafford Medical School Scholarship Award
1987	Honors in Pediatrics, Columbia University, College of Physicians & Surgeons
1991	Outstanding Teaching of Medical Students Award, University of Rochester
1992-1994	Innovations in Patient Care Grant, Intramural clinical research grant
1992-95	Multidisciplinary Training in Pulmonary Research #HL 07216, NIH-sponsered training grant
1997-99	ALA Grant "The effect of mechanical strain on pulmonary epithelial cell signaling and proliferation".

PUBLICATIONS

Chess P, Ryan R, Finkelstein J. Tyrosine kinase activity is necessary for rabbit type II cell proliferation. Pediatr Res;36:481-486,1994.

Gaspari A, Sempowski G, Chess P, Gish J, Phipps R. Human epidermal keratinocytes are induced to secrete IL-6 and co-stimulate T-lymphocytes proliferation by a CD40-dependent mechanism. Eur J Immunol; 26:1371-1377, 1996.

Sempowski G, Chess P, Moretti A, Paoilla J, Linares A, Phipps R, Blieden T. CD40 mediated activation of gingival and periodontal ligament fibroblasts. J Periodontol 68:284-292, 1997.

Chess P, Chess M, Manuli M, Guillet R. Indications for screening head ultrasounds in very low birthweight infants. Pediatr Radiol; 27: 305-308, 1997.

Sempowski G, Chess P, Phipps R. CD40 is a functional activation antigen and B7-independent T cell costimulatory molecule on normal human lung fibroblasts. J Immunol 158:4670-4677, 1997.

Chess P, D'Angio C: Clonic movements following Lorazepam administration in full term infants. *Archives Pediatric Adolescent Med*, 152:98-99 (1998).

Chess PR, Ryan RM, Finkelstein JN: H441 pulmonary epithelial cell mitogenic effects and signaling pathways in response to HGF and TGFα. *Experimental Lung Research*, 24:27-39 (1998).

Shrier D, Wang A, Patel U, Monajati A, Chess P, Numaguchi Y. Benign fibrous histiocytoma of the nasal cavity in a newborn: MR and CT findings. *Am J Neuroradiol* 19;1166-1168 (1998).

Khalak R, Chess P: Fulminant necrotizing enterocolitis in a premature neonate treated for supraventricular tachycardia. *J Perinatology*, 18;306-307 (1998).

Maniscalco W, Watkins R, Chess P, Sinkin R, Horowitz S, Toia L: Cell-specific expression of fibronectin and the EIIIA and EIIIB splice variants after oxygen injury. *Amer J Physiology*, 274:L599-L609 (1998).

Sinkin RA, Dweck HS, Horgan MJ, Gallaher KJ, Cox C, Maniscalco WM, Chess PR, D'Angio CT, Guillet R, Kendig JW, Ryan RM, Phelps DL. Early dexamethasone- Attempting to prevent chronic lung disease. *Pediatrics*, 105:542-548 (2000).

Chess P, Toia L, Finkelstein J. Mechanical strain induced proliferation and signaling in pulmonary H441 cells. In press, *Amer J Physiology* (2000).

Bhatt A, Amin S, Watkins R, Chess P, Maniscalco W. Expression of Vascular Endothelial Growth Factor and Flk-1 in Developing and Glucocorticoid-Treated Mouse Lung. In press, *Pediatric Research* (2000).

Uy I, Pryhuber G, Chess P, Notter R, "Combined-modality therapy with inhaled nitric oxide and exogenous surfactant in term infants with acute respiratory failure." In press, *Pediatr Crit Care Med,* (2000).

Miller CE, Donlon KJ, Toia L, Wong CL, Chess PR: Cyclic strain induces proliferation of cultured embryonic heart cells. Submitted for publication, *Circulation Research* (2000).

BOOK CHAPTERS

Pending Publication

ABSTRACTS/ PRESENTATIONS (LAST THREE YEARS)

Chess P, Toia L, Finkelstein J: The effect of mechanical strain on pulmonary epithelial cell signaling and proliferation. Am J Respir Crit Care Med 155:A610 (1997).

Chess PR, Watkins R, Maniscalco WM: Regulation of vascular endothelial growth factor expression in pulmonary epithelial cells. Am J Respir Crit Care Med 157:A454 (1998).

Miller CE, Donlon KJ, Toia L, Wong CL, Chess PR: Cyclic stretch induces proliferation of embryonic myocytes and fibroblasts. Biomedical Engineering Society Annual Meeting, (1998).

Bhatt AJ, Watkins RH, Chess PR, Maniscalco WM: Dexamethasone induces Vascular endothelial growth factor and Hypoxia inducible factor- like factor mRNA in newborn mice. Am. J. Respir. Crit. Care Med. 159: A900, (1999).

Bhatt AJ, Watkins RH, Chess PR, Maniscalco WM: Vascular endothelial growth factor (VEGF), VEGF receptor (FLK-1) and Hypoxia inducible factor- like factor mRNA abundance are increased by dexamethasone in postnatal mouse lung. Pediatr Res. 45: A275, (1999).

Chess PR, Donlon KJ, Toia L, Wong CL, Miller CE. Cyclic strain induced proliferation and signaling in embryonic cardiocytes, Am. J. Respir. Crit. Care Med. 161:A (2000).

Carroll SL, Chess PR. Outcome of near-term infants- implication of preterm delivery at 34-37 weeks gestation on pulmonary morbidity. Am. J. Respir. Crit. Care Med. 161:A (2000).

Chess PR, Toia L, VanWuyckhuyse B. Characterization and partial sequencing of a high molecular weight protein activated in response to mechanical strain in pulmonary epithelial cells. Am. J. Respir. Crit. Care Med. 161:A (2000).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Carl T. D'Angio	Assistant Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Princeton University, Princeton, NJ	A.B.	1979	English
Johns Hopkins University, Baltimore, MD	M.D.	1983	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1983-1984 Contract Physician, Wardenburg Student Health Center, University of Colorado, Boulder, CO. (Concurrent training for Olympic Trials Marathon)
1984-1987 Pediatric Residency, The Children's Hospital of Philadelphia, Philadelphia, PA
1987-1988 Registrar in Pediatrics, Professorial Unit, The Hospital for Sick Children, Great Ormond Street, London, ENGLAND
1988-1989 Staff Pediatrician, Fort Defiance Indian Hospital, Lieutenant, US Public Health Service, Fort Defiance, AZ
1989-1991 Chief of Pediatrics, Fort Defiance Indian Hospital, Lieutenant Commander, US Public Health Service, Fort Defiance, AZ
1991-1994 Instructor and Fellow in Neonatology, University of Rochester School of Medicine, Rochester, NY
1994-1995 Senior Instructor in Neonatology, University of Rochester School of Medicine, Rochester, NY
1995-present Assistant Professor of Pediatrics, University of Rochester School of Medicine, Rochester, NY.

HONORS

The PHS Citation, US Public Health Service, 1991.
Buswell Fellowship Award, University of Rochester, 1999-2000.

SELECTED PUBLICATIONS

D'Angio C, Ruz J, Eichenberg CS, Varian D. Evaluation of patient advocacy in a major urban emergency room. **Proc Amer Stat Assoc (Social Statistics Section)** 1980:263-265.

D'Angio CT, McGowan KL, Baumgart S, St Geme J III, Harris MC. Surface colonization with coagulase-negative staphylococci in premature neonates. **J Pediatr** 1989; 114:1029-1034.

D'Angio CT and Lloyd JK. Nephrocalcinosis in Shwachman's syndrome. **Arch Dis Child** 1989; 64:614-615.

St Geme JW III, Bell LM, Baumgart S, D'Angio CT, Harris MC. Distinguishing sepsis from blood culture contamination in young infants with blood cultures growing coagulase-negative staphylococci. **Pediatrics** 1990; 86:157-162.

D'Angio CT, Dillon MJ, Leonard JV. Renal tubular dysfunction in methylmalonic acidemia. **Eur J Ped** 1991; 150:259-263.

D'Angio CT, Sinkin RA, LoMonaco MB, Finkelstein JN. Interleukin-8 and monocyte chemoattractant protein-1 mRNAs in oxygen injured rabbit lung. **Am J Physiol** 1995; 268(12):L826-L831.

D'Angio CT, Maniscalco WM, Pichichero ME. Immunologic response of extremely premature infants to tetanus, *Haemophilus influenzae* and polio immunizations. **Pediatrics** 1995; 96:18-22.

D'Angio CT, Froehlke RF, Plank G, Meehan DJ, Aguilar CM, Lande MB, Hugar L. Long term outcome of *Haemophilus influenzae* meningitis in Navajo Indian children. **Arch Ped Adol Med** 1995; 149:1001-1008.

Daly H, Baecher-Allen C, Barth R, D'Angio CT, Finkelstein JN. Bleomycin induces strain-dependent alterations in the pattern of epithelial cell-specific marker expression in the mouse lung. **J Tox Appl Pharm** 1997; 142:303-310.

D'Angio CT, Finkelstein JN, LoMonaco MB, Paxhia A, Wright SA, Baggs RB, Notter RH, Ryan RM. Changes in surfactant protein gene expression in a neonatal rabbit model of hyperoxia-induced fibrosis. **Am J Physiol 1997;** 272(16):L720-L730.

Maniscalco WM, Watkins RH, D'Angio CT, Ryan RM. Hyperoxic injury decreases alveolar epithelial cell expression of vascular endothelial growth factor (VEGF) in neonatal rabbit lung. **Am J Resp Cell Mol Biol** 1997; 16:557-567.

Ambati J, Chalam KV, Chawla DK, D'Angio CT, Guillet EG, Rose SJ, Vanderlinde RE, Ambati BK. Elevated gamma-aminobutyric acid, glutamate and vascular endothelial growth factor levels in the vitreous of patients with proliferative diabetic retinopathy. **Arch Ophth** 1997; 115:1161-1166.

Chess PR, D'Angio CT. Stereotypic movements following lorezepam administration in full-term infants. **Arch Ped Adol Med** 1998; 152:98-99.

Khalak R, Pichichero ME, D'Angio CT. Three year follow-up of vaccine response in extremely premature infants. **Pediatrics** 1998; 101:597-603.

D'Angio CT, Johnston CJ, Wright TW, Reed CK, Finkelstein JN. Chemokine mRNA alterations in newborn and adult mouse lung during acute hyperoxia. **Exp Lung Res** 1998; 24:685-702.

Charafeddine L, D'Angio CT, Richards JL, Stripp BR, Finkelstein JN, Orlowski CC, LoMonaco MB, Paxhia A, Ryan RM. Hyperoxia increases keratinocyte growth factor mRNA expression in neonatal rabbit lung. **Am J Phys** 1999; 276:L105-L113.

Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease patterns in neonates. **Pediatr** 1999; 103:759-765.

Watkins R, D'Angio CT, Ryan RM, Maniscalco WM. Differential expression of VEGF mRNA splice variants in newborn and adult hyperoxic lung injury. **Am J Physiol** 1999; 20:L858-L867.

D'Angio CT, LoMonaco MB, Chaudhry SA, Paxhia A, Ryan RM. Discordant pulmonary proinflammatory cytokine expression during acute hyperoxia in the newborn rabbit. **Exp Lung Res** 1999; 25:443-465.

D'Angio CT, Maniscalco WM, Ryan RM, Avissar NE, Basavegowda KP, Sinkin RA. Vascular endothelial growth factor (VEGF) in pulmonary lavage fluid from preterm infants: effects of age and postnatal dexamethasone. **Biol Neonate** 1999; 76:266-273.

Sinkin RA, Dweck HS, Horgan MJ, Gallaher KJ, Cox C, Maniscalco WM, Chess PR, D'Angio CT, Guillet R, Kendig JW, Ryan RM, Phelps DL. Early dexamethasone - attempting to prevent chronic lung disease. **Pediatr** 2000; 105:542-548.

Book Chapters and Review Articles

D'Angio CT. Immunization of the premature infant. Pediatr Infect Dis J 1999; 18:824-825.

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Ronnie Guillet	Associate Professor in Neonatology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
State University of New York at Albany	B.S.	1973	Biology
University of Rochester, Rochester, NY	M.S.	1975	Biophysics
University of Rochester, Rochester, NY	Ph.D.	1980	Biophysics
University of Rochester, Rochester, NY	M.D.	1980	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1983-1985 Instructor, Dept of Pediatrics, Univ of Pennsylvania School of Medicine, Philadelphia, PA
1988-1991 Research Assoc/Asst Professor, (PT), Dept of Psychology, Univ Rochester, Rochester, NY
1991-1997 Assistant Professor, Division of Neonatology, Dept Pediatrics, Strong Memorial Hospital, Rochester, NY
1997-pres Associate Professor, Division of Neonatology, Dept Pediatrics, Children's Hospital at Strong, Rochester, NY
1991-pres Chief of Pediatrics, Highland Hospital, Rochester, NY

ACADEMIC AWARDS AND HONORS

1972 National Science Foundation Undergraduate Research Program Grant
1973 B.S., Cum Laude in Biology
1973 NIH Biophysics Training Grant (Four years) #5 TO1 GM01088
1976 NIH Medical Scientist Training Grant (Four years) #T 05 GM 02263
1977 Doctoral Thesis: "The development of the adrenal axis in the neonatal rat." Univ Rochester, Rochester, NY
1985 NIDA - Postdoctoral Fellowship # T32DA07232
1992 Member, Society for Pediatric Research

PUBLICATIONS (Previous three years plus earlier representative publications):

Kellogg CK, Guillet R. Developmental effects of neuroactive drugs. In: Transplacental effects on fetal health. G. Migaki (Ed.) Progress in Clinical and Biological Research 281:265-277, 1988. Alan R. Liss, Inc., NY.

Miranda R, Ceckler T, Guillet R, Kellogg C. Early developmental exposure to benzodiazepine ligands alters brain 31P-NMR spectra in young adult rats. Brain Research 506:85-92, 1990.

Miranda R, Ceckler T, Guillet R, Kellogg CK. Aging-related changes in brain metabolism are altered by prenatal exposure to diazepam. Neurobiol Aging 11:117-122, 1990.

Guillet R. Neonatal caffeine exposure alters adenosine receptor control of locomotor activity in the developing rat. Devel Pharm Therapeut 15:94-100, 1990.

Guillet R, Kellogg C. Neonatal therapeutic caffeine exposure alters the ontogeny of brain adenosine A1 receptors in rats. Neuropharmacol 30:489-496, 1991.

Guillet R, Kellogg CK. Neonatal caffeine exposure alters developmental sensitivity to adenosine receptor ligands. Pharmacol Biochem Behav 40:811-817, 1991.

Guillet R. Animal models for caffeine exposure in the perinatal period. In: Neuromethods, Vol. 24: Animal Models of Drug Addiction. A.A. Boulton, G.B. Baker and P.H. Wu (eds.) The Humana Press Inc., NJ (1992), pp. 383-423.

Etzel B, Guillet R. Effects of neonatal exposure to caffeine on adenoisne A1 receptor ontogeny using autoradiography. Dev Brain Res 82:223-230, 1994.

Guillet R, Dunham L. Neonatal caffeine exposure and seizure susceptibility in adult rats. Epilepsia 36:743-749, 1995.

Stevens TP, Guillet R. Use of glucagon to treat neonatal low-output congestive heart failure following maternal labetalol therapy: A case report. J Pediatr 127:151-153, 1995.

Guillet R. Neonatal caffeine exposure alters seizure susceptibility in rats in an age-related manner. Dev Brain Res 89:124-128, 1995.

Chess P, **Guillet R.** Screening head ultrasounds to detect intraventricular hemorrhage in premature infants. Pediatric Radiology 27:305-308, 1997.

Fisher S, **Guillet R.** Neonatal caffeine alters passive avoidance retention in rats in an age- and gender-related manner. Dev Brain Res 98:145-149, 1997.

Laroia N, McBride L, Baggs R, **Guillet R.** Dextromethorphan ameliorates effects of neonatal hypoxia on brain morphology and seizure threshold in rats. Dev Brain Res 100:29-34, 1997.

Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, **Guillet R**, Cox C, Dweck HS, Horgan MJ, Reubens LJ. Risemberg H, Phelps DL. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. [Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial] Pediatrics. 101(6):1006-12, 1998 Jun.

Butler-O'Hara M, LeMoine C, **Guillet R**. Analgesia for neonatal circumcision: A randomized controlled trial of EMLA cream versus dorsal penile nerve block. Pediatrics 101:electronic pages, 1998.

Laroia N, **Guillet R**, Burchfiel J, McBride MC. EEG background as predictor of electrographic seizures in high-risk neonates. Epilepsia 39:545-551,1998.

Amin SB, Orlando MS, Dalzell LE, Merle KS, **Guillet R**. Morphological changes in serial auditory brainstem responses (ABRs) in 24-32 weeks gestational age infants during the first week of life. Ear and Hearing 20:410-418, 1999.

Sinkin RA, Dweck HS, Horgan MJ, Gallaher KJ, Cox C, Maniscalco WM, Chess PR, D'Angio CT, **Guillet R**, Kendig JW, Ryan RM, Phelps DL. Early dexamethasone - Attempting to prevent chronic lung disease. Pediatrics 105:542-548, 2000.

Amin SB, Merle KS, Orlando MS, Dalzell LE, **Guillet R**. Brainstem maturation in premature infants as a function of enteral feeding type. Pediatrics, in press (November, 2000).

McBride MC, Laroia N, **Guillet, R**. Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. Neurology, in press.

ABSTRACTS

Amin SB, Dalzell LE, Orlando M, Merle KS, **Guillet R**. Brain maturation may be more rapid in breast fed preterm infants. Pediatr Res, 40:163A, 1998.

Amin SB, Merle KS, Orlando M, Dalzell LE, Johnson L **Guillet R**. Bilirubin:albumin ratio in transient bilirubin encephalopathy as evaluated by BAER in premature infants. Pediatr Res, 40:255A, 1998.

Amin SB, Ahlfors CE, Orlando MS, Merle KS, Dalzell LE, **Guillet R**. Unbound bilirubin predicts encephalopathy in premature infants. Pediatr Res, 45:181A, 1999.

Amin SB, Charafeddine L, **Guillet R**. Transient bilirubin encephalopathy can manifest as apnea of prematurity. Pediatr Res, 45:181A, 1999.

Laroia N, McBride M, **Guillet R**. Neonatal electrographic seizure burden correlates with neurologic outcome. Pediatr Res, 45:344A, 1999.

Uy IP, Menegus M, D'Angio CT, **Guillet R**. Changes in early onset Group B hemolytic streptococcus disease with changing recommendations for prophylaxis. Pediatr Res 47:348A, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Nirupama Laroia	Fellow and Instructor in Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Government College, Simla, Himachal Pradesh, INDIA	B.Sc.1	1973	Biology
Christian Medical College, Ludhiana, Punjab, INDIA	MBBS	1980	Medicine
Institute of Medical Sciences, Banaras Hindu Univ Varanasi, U.P., INDIA	MD	1984	Pediatrics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1980 - 1981	SHO. Ob/Gyn, Christian Medical College and Hospital, Ludhiana, Punjab
1981 - 1984	Resident (Pediatrics), Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.
1985 - 1986	Senior Resident (Pediatrics), Ram Manohar Lohia Hospital, New Delhi, India
1986 - 1988	Maternity leave and Period of transition in the move to the United Kingdom
1988 - 1989	SHO. Pediatrics, Odstock Hospital, Salisbury, Wiltshire, U.K.
1989 - 1989	SHO. Pediatrics (Locum), Lincoln County Hospital, Lincoln, U.K.
1989 - 1990	CMO./Senior S.H.O. in Community Health and Pediatrics, Lincoln County Hospital, Lincoln, U.K.
1990 - 1990	SHO. Neonatology, Hammersmith Hospital, London, U.K.
1991 - 1991	SHO.PediatricRotation,NeonatalUnitLeicesterGeneralHospital,Leicester, U.K., General Pediatrics, Leicester Royal Infirmary, Leicester, U.K.
1991 - 1992	Registrar Pediatrics, Walsgrave Hospital, Coventry, U.K.
1992 - 1993	Neonatal Research, Neonatal- Perinatal Medicine, Department of Pediatrics, Medical College of Virginia, Richmond, Virginia.
1993 - 1994	Pediatric Resident PL-3, Department of Pediatrics, Medical College of Virginia, Richmond, Virginia.
1994 - 1998	Fellow, Neonatal-Perinatal Medicine, Department of Pediatrics, Strong Memorial Hospital Rochester, NY
1998-pres	Assistant Professor, Department of Pediatrics, Division of Neonatology, Children's Hospital at Strong, University of Rochester, Rochester, NY.
1999-pres	Medical Director, Special Care Nursery & Section Chief, Neonatology, Rochester General Hospital, Rochester, NY.

HONORS AND AWARDS

1995	Wyeth Neonatology Research Grant: "A Randomized Trial of Treatment of Neonatal Seizures with Lorazepam and Phenobarbital," $3400.00
1995	Dorothea Haus Ross Foundation $6000.00 towards funds for hardware - Computerized Neonatal EEG analysis.
1996	Bradford Fellowship, University of Rochester. Rochester, NY
1996	Savoy Junior Fellowship. Fellowship award to travel and present at the Eastern Assoc. of Electroencephalographers, Inc. St. Saveur, Quebec, Canada.

PUBLICATIONS

Laroia, N. Current controversies in diagnosis and management of neonatal seizures. Editorial. Indian Pediatrics 2000;37:367-372.

Pending Publication

Pending Publication

Laroia, N., Guillet, R., Birchfiel, J., McBride, M. EEG Background as Predictor of Electrographic Seizures in High- Risk Neonates. Epilepsia. 39(5):545-551,1998.

Laroia, N., McBride, L., Baggs, R., Guillet, R. Dextromethorphan ameliorates effects of neonatal hypoxia on brain morphology and seizure threshold in rats. Dev Brain Res. 100:29-34. 1997.

ABSTRACTS

N. Laroia, M. McBride, R. Guillet, J. Birchfiel. EEG Background Predicts Electrical Seizures in High Risk Neonates. Presented at the Eastern Association of Electroencephalographers, Inc., St Sauveur, Quebec, Canada. Feb 1996. Electroencephalography and Clinical Neurophysiology, 1996.

N. Laroia and R. Guillet. Dextromethorphan (DM) Ameliorates Effects of Neonatal Hypoxia on Brain Morphology and Seizure Threshold in Rats. Society for Pediatric Research, Washington D.C., May 1996. Pediatric Research 39: 376a, 1996.

N. Laroia, M. McBride, R. Guillet. Neonatal Electrical Seizures are Often Clinically Inapparent and Resistant to Treatment. Society for Pediatric Research, Washington D.C., May 1996. Pediatric Research 39:376a, 1996.

N. Laroia, H. Gelbard, R. Guillet. Apoptosis Causes cell loss in the cerebral cortex after hypoxial injury in rats. Society for Pediatric Research, Washington, D.C. May 1997. Pediatric Research 40, 1997.

N. Laroia, M. McBride, R. Guillet. Neonatal Electrographic Seizure Burden Correlates with Neurologic Outcome. Pediatric Research 45:344A, 1999.

N. Laroia, M. McBride, R. Guillet. Pharmacokinetics of Felbamate in Infants with Hypoxic Ischemic Encephalopathy. Pediatric Research 46, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Ruth Lawrence	Professor of Pediatrics, Obstetrics & Gynecology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Antioch College, Antioch, Ohio, Summa Cum Laude Distinction	B.S.	1945	Biology
University of Rochester School of Medicine, Rochester, New York	M.D.	1949	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL TRAINING AND EXPERIENCE

1949-50 Intern and Resident in Pediatrics, Yale University School of Medicine, Grace New Haven Community Hospital
1950-51 Assistant Resident in Medicine, Grace New Haven Community Hospital
1951 Fellowship, Room-In Project, Edith M. Jackson, M.D., Pediatrics, Yale New Haven Hospital
7/51-10/51 Chief Resident, Newborn Service, Yale New Haven Hospital
1/52-7/52 Consultant in Medicine, United States Army, Fort Dix, New Jersey
7/52-7/58 Research Pediatrician, Monroe County Health Department, Rochester, New York
1952-60 Clinical Instructor in Pediatrics, University of Rochester
1957-58 Associate Resident and Instructor in Pediatrics, University of Rochester
1960-64 Senior Instructor in Pediatrics, University of Rochester
1964-70 Assistant Professor of Pediatrics, University of Rochester
1970-85 Associate Professor of Pediatrics, University of Rochester
1975-85 Associate Professor of Obstetrics and Gynecology, University of Rochester
1985- Professor of Pediatrics and Professor of Obstetrics and Gynecology, University of Rochester

PUBLICATIONS (Selected since 1959)

1. Lawrence RA, Haggerty RJ. Household agents and their potential toxicity. *Mod Treatment* 4:633-647, 1967.
2. Lopate C. Women for Medicine. Baltimore: The Johns Hopkins Press, 1968 (Editorial Consultant).
3. Lawrence RA, Haggerty RJ. Household agents and their potential toxicity. *Modern Treatment* 8:511-527, 1971 (also published in Spanish and Italian).
   Lawrence RA. "Normal Newborn"; "Infant Feeding"; and "Childhood Poisoning and Accidents". *The Merck Manual,* Thirteenth Edition, 1975. Updated for Fourteenth Edition, 1980. Updated for Fifteenth Edition, 1989. Updated for Sixteenth Edition, 1990. Updated for Seventeenth Edition, 1998.
4. Lawrence RA. Infants of adolescent mothers: perinatal, neonatal and infancy outcome. In: McAnarney ER (Ed). *Premature adolescent pregnancy and parenthood.* New York: Grune and Stratton, Inc., p. 149-168, 1983.
5. Lawrence RA. Early mothering by adolescents. In: McAnarney ER (Ed). *Premature adolescent pregnancy and parenthood.* New York: Grune and Stratton, Inc., p. 207-218, 1983.
6. Lawrence RA (Chair). Human lactation as a physiologic process. In: *Report of the Surgeon General's Workshop on Breastfeeding and Human Lactation.* Editorial, Department of the National Center for Education in Maternal and Child Health: Anthony Waddell, Director of Publications (Ed), 1984.
7. Lawrence RA. Approach to breastfeeding. In: Walker WA and Watkins J (Eds). *Nutrition in pediatrics-basic sciences and clinical application.* Boston: Little, Brown & Co., 1984.
8. Lawrence RA. *Contemporary issues in maternal and child Health and nutrition: an interprofessional conference,* Vancouver, British Columbia, Canada, May 7-9, 1986. Proceedings published, Medical Education Services (Canada) Inc.
9. Lawrence RA. Maternal factors in lactation failure. In: Hamosh M, Goldman A (Eds). *Human Lactation III.* Plenum Press, New York, 1987.
10. Lawrence RA (Ed.) Breastfeeding. *Clinics in Perinatology* 32, 1987.

11. Lawrence RA. The management of lactation as a physiologic process. *Clinics in Perinatology* 32:1-10, 1987.
12. Lawrence RA. Major difficulties in promoting breastfeeding: US perspectives. In: *Programmes to Promote Breastfeeding,* Jelliffe DB, Jelliffe ER (Eds). Oxford Medical Publications, pp. 267-278, 1988.
13. Lawrence RA. Breastfeeding and medical disease. *Medical Clinics of North America* 73:583-604, 1989.
14. Lawrence RA. The Puerperium, breastfeeding, and breast milk, *Current Opinions on Obstetrics & Gynecology* 2:2:23- 30, 1990.
15. Hamosh M, Dewey KG, Garza C, Goldman AS, Lawrence RA, Picciano MF, Quandt SA, Rasmussen KM, Rush D. *Nutrition during lactation,* Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, National Academy Press, Washington, D.C., February 1991.
16. Lawrence RA. Corticosteroid effect on lactation. *JAMA* 265:2409, 1991.
17. Lawrence RA. Choosing to breastfeed: a national challenge. Will it become American to breastfeed? *Birth* 18:226-227, 1991.
18. Rosen AR, Lawrence RA. The effect of Epidural anesthesia on infant feeding. *JURMC* 6:1:3-7, Spring 1994.
19. Lawrence RA. Early discharge alert. *Pediatrics* 96:5:966, 1995.
20. Lawrence RA. Lactation, breastfeeding, infant care and mental illness. In: *Handbook of behavioral obstetrics & gynecology,* Kuczmierczyk AR and Reading AE (Eds.), Plenum Press, NY, 1995.
21. Lawrence RA. Breastfeeding. In: Carlson, Eisenstat (Eds). *Primary care of women,* C.V. Mosby, 1995.
22. Lawrence RA. Breast-Feeding. In: Epps RP, Stewart SC. *The Women's Complete Healthbook,* Delacorte Press, The Philip Lief Group, Inc., New York, p. 281-289, 1995.
23. Lawrence RA, Friedman LR. Drugs and contaminants in human milk. In Jensen RG and Jenness R (Eds.) *Handbook of milk composition,* Academic Press Inc., Harcourt, Brace, Jovanovich Pub, 1995.
24. Lawrence RA. Breast-Feeding. In: Epps RP, Stewart SC (Eds). *The American Medical Women's Association Guide to Pregnancy and Childbirth,* Bantam Doubleday Dell Publishing Group, Inc., p. 145-167, 1996.
25. Lawrence RA. Approach to breastfeeding. In: Walker WA and Watkins J (Eds). *Nutrition in pediatrics-basic sciences and clinical application,* 2nd Edition, Boston: Little, Brown & Co., 458-473, 1996.
26. Lawrence RA. *A review of the medical benefits and contraindications to breastfeeding in the United States* (Maternal and Child Health Technical Information Bulletin). Arlington, VA:National Center for Education in Maternal and Child Health, 1997.
27. Lawrence RA. Breastfeeding. In: Blechman EA, Brownell KD (Eds). *Behavioral Medicine & Women.* The Guilford Press:New York, 495-500, 1998.
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29. Lawrence RA. Poison centers and plants: More Pollyanna data? *Clinical Toxicology* 36(3):225-226, 1998.
30. Lawrence RA, Lawrence RM. *Breastfeeding: a guide for the medical profession,* First Edition, Second Edition, Third Edition, Fourth Edition, Fifth Edition, St. Louis: C.V. Mosby, 1980, 1985, 1989, 1994, 1998.
31. Lawrence RA. Milk banking: the influence of storage procedures and subsequent processing on immunological components of human milk. In: Draper HH, Woodward W (Eds) *Advances in Nutritional Research* (In Press).
32. Lawrence RA. *Breastfeeding: a guide for the medical profession,* 5th Edition, St. Louis: C.V. Mosby, 1999.\
33. 26.Howard CR, Howard FM, Lawrence RA, et. al. The effects of early pacifier use on breastfeeding duration. *Pediatrics* 103:3:E33, 1999.
34. Schanler RJ, O'Connor KG, Lawrence RA. Pediatricians' practices and attitudes regarding breastfeeding promotion. *Pediatrics* 103:3:E35, 1999.
35. Lawrence RA, Howard CR. Given the benefits of breastfeeding, are there any contraindications? *Clinics in Perinatology* 26:479, 1999.
36. Lawrence RA. Storage of human milk and the influence of procedures on immunological components of human milk. *Acta Paediatrica* 430:1, 1999.
37. Howard CR, Lawrence RA. Drugs and breastfeeding. *Clinics in Perinatology* 26:447, 1999.
38. Pending Publication
39. Pending Publication
40. Pending Publication
41. Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
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NAME	POSITION TITLE
William M. Maniscalco	Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Massachusetts, Amherst, MA	B.A.	1968	Liberal Arts
Johns Hopkins University, Baltimore, MD	M.D.	1972	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1972-1975 Intern, Resident and Senior Resident in Pediatrics, Children's Hospital Medical Center, Boston, Massachusetts

1975-1977 Postdoctoral Fellow, Pediatrics (Neonatology), Yale University School of Medicine, New Haven, Connecticut

1977-1978 Senior Research Fellow in Neonatology, Yale University School of Medicine, New Haven, Connecticut

1978-1984 Assistant Professor, Pediatrics and Obstetrics/Gynecology, University of Rochester School of Medicine, Rochester, New York

1984-1994 Associate Professor, Pediatrics, University of Rochester School of Medicine, Rochester, New York

1994- Professor of Pediatrics, University of Rochester School of Medicine, Rochester, NY

SELECTED PUBLICATIONS

Maniscalco WM, Finkelstein JN, Parkhurst AB. De novo fatty acid synthesis by freshly isolated alveolar type II epithelial cells. *Biochim Biophys Acta* 751:462-469, 1983.

Finkelstein JN, Maniscalco WM, Shapiro DL. Properties of freshly isolated type II alveolar epithelial cells. *Biochim Biophys Acta* 762:398-404 1983.

Maniscalco WM, Finkelstein JN, Parkhurst AB. Dexamethasone increases de novo fatty acid synthesis in fetal rabbit lung explants. *Pediatric Research* 19:1272-1277 1985.

Shapiro DL, Livingston JN, Maniscalco WM, Finkelstein JN. Insulin receptors and insulin effects on type II alveolar epithelial cells. *Biochimica et Biophysica Acta* 885:216-220 1986.

Kendig JW, Notter RH, Cox C, Aschner JL, Benn S, Bernstein RM, Hendricks-Munoz K, Maniscalco WM, Metlay LA, Phelps DL, Sinkin RA, Wood BP, Shapiro DL. Surfactant replacement therapy at birth: final analysis of a clinical trial and comparisons with similar trials. *Pediatrics* 82:756-62, 1988.

Maniscalco WM, Finkelstein JN, Parkhurst A. Effects of exogenous fatty acids and inhibition of *de novo* fatty acid synthesis on disaturated phosphatidylcholine production by fetal lung cells and adult type II cells. *Exp Lung Res* 15:473-89, 1989.

Maniscalco WM, Stremmel W, Heeney M. Uptake of palmitic acid by rabbit alveolar type II cells. *Am J Physiol: Lung Cell Mol Physiol* 259:L206-212, 1990.

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, Sinkin RA, Bartoletti A, Dweck HS, Horgan MJ, Risenberg H, Phelps DL, Shapiro DL. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. *N Engl J Med* 324:865-71, 1991.

Maniscalco WM, Campbell MH. Alveolar type II cells synthesize hydrophobic cell-associated proteoglycans with multiple core proteins. *Am J Physiol:Lung Cell Mol Physiol* 1992 Sep;263:L348-56.

Maniscalco WM, Campbell MH. Transforming growth factor-β induces a chondroitin sulfate/dermatan sulfate proteoglycan in alveolar type II cells. *Am J Physiol:Lung Cell Mol Physiol* 1994; 266:L672-L680.

Piedboeuf B, Maniscalco WM, Hall S, Campbell M, Watkins R, Horowitz S. In vivo and in vitro expression of metallothionein in injured type II alveolar epithelial cells. *Chest* 1994; 105(3 Suppl):78S.

Maniscalco WM, Sinkin RA, Watkins RH, Campbell MH. Transforming growth factor-β modulates type II cell expression of fibronectin and surfactant protein C. *Am J Physiol: Lung Cell Mol Physiol*, 1994; 267:L569-L577.

Maniscalco WM, Watkins RH, Finkelstein JN, Campbell MH. Vascular endothelial growth factor mRNA increases in alveolar epithelial cells during recovery from oxygen injury. *Am J Resp Cell Mol Biol* 1995; 13:377-386.

Hudak ML and the Surfactant Study Group (WM Maniscalco PI for Univ. of Rochester). A multicenter randomized masked comparison trial of natural surfactant v. synthetic surfactant for he treatment of respiratory distress syndrome. *J Pediatrics* 1996; 128:396-406.

Maniscalco WM, Watkins RH, Campbell MH. Expression of fibronectin mRNA splice variants by rabbit lungs *in vivo* and by alveolar type II cells *in vitro*. *Am J Physiol:Lung Cell Mol Physiol* 1996; 271: L972-L980.

Maniscalco WM, Watkins RH, D'Angio CT Ryan RM Hyperoxic injury decreases alveolar epithelial cell expression of vascular endothelial growth factor (VEGF) in neonatal rabbit lung. *Am J Resp Cell Mol Biol* 1997;16:557-567.

Veness-Meehan KA, Moats-Staats BM, Maniscalco WM, Watkins RH, Stiles AD. Changes in decorin expression with hyperoxic injury to developing rat lung. *Pediatr Res* 1997; 41:464-472.

Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens LJ, Risemberg H, Phelps D. Comparison of two strategies for surfactant prophylaxix in very premature infants: a multicenter randomized trial. *Pediatrics* 1998; 101:1006-1012.

Maniscalco WM, Watkins RH, Chess PR, Horowitz S, Toia L. Lung cell-specific expression of fibronectin and the EIIIA and EIIIB splice variants after oxygen injury. *Am J Physiol: Lung Cell Mol Physiol* 1998, L599-L609.

O'Reilly MA, Staversky RJ, Watkins RH, Maniscalco WM. Accumulation of $p21^{cip/waf1}$ during hyperoxic lung injury. *Am J Resp Cell Mol Biol* 1998; 19: 777-785.

Watkins, RH, D'Angio, CT, Ryan, RM, Paltel, A, Maniscalco, WM. Differential expression of VEGF mRNA splice variants in newborn and adult hyperoxic lung injury. *Am J Physiol: Lung Cell Mol Physiol* 276:L858-L867, 1999.

D'Angio CT, Maniscalco WM, Ryan RM, Avissar NE, Basavegowda K, Sinkin RA. Vascular endothelial growth factor (VEGF) in pulmonary lavage fluid from premature infants: effects of age and postnatal dexamethasone. Biol Neonate 76:266-273, 1999.

Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. RSV-associated hospitalization and economic implications for premature infants born <32 weeks gestation. *Archives Ped Adol Med* 154:55-61, 2000.

Pending Publication

Pending Publication

Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Gloria Salvini Pryhuber M.D.	Assistant Professor

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Cornell University, Ithaca, N.Y.	B.S.	1981	Biology
SUNY Health Science Center, Syracuse, N.Y.	M.D.	1985	Medicine
SUNY Health Science Center, Syracuse, N.Y.	Residency	1988	Pediatrics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PREVIOUS EMPLOYMENT

1988-1991 Fellowship in Neonatology, University of Cincinnati Medical Center, Cincinnati, Ohio
1991-1994 New Investigator, Program of Excellence in Molecular Biology of the Heart and Lung Cincinnati, Ohio
1991-1994 Pediatric Procter Research Scholar, Children's Hospital Medical Center, Cincinnati, Ohio
1994-1997 Assistant Professor of Pediatrics, Children's Hospital at Strong, Univ Rochester, Rochester NY
1997-Pres Assistant Professor of Pediatrics and Environmental Medicine, Univ Rochester, Rochester NY

HONORS

1981 B.S. with distinction, Cornell University, Ithaca, N.Y.
1985 M.D., cum laude, SUNY Health Science Center , Syracuse, N.Y.
1985&1986 Resident Teaching Award, SUNY Health Science Center, Syracuse, N.Y.
1985 Alpha Omega Alpha Medical Honor Society
1985 Janet M. Glascow Memorial Achievement Award, American Medical Women's Association SUNY Health Science Center, Syracuse, N.Y.
1987 Assistant Chief Resident in Pediatrics, SUNY Health Science Center , Syracuse, N.Y.
1989 Chief Fellow in Neonatology, University of Cincinnati Medical Center,Cincinnati,Ohio
1995 Buswell Research Fellowship Award, University of Rochester, Rochester, New York

PUBLICATIONS

Pryhuber, G.S., O'Reilly, M. A., Clark, J.C., Hull, W.M., Fink, I. and Whitsett, J.A. Phorbol Ester inhibits surfactant protein SP-A and SP-B expression. J Biol Chem 265(34), 20821-20828, 1990.

Pryhuber, G.S., Hull, W.M., Fink, I., McMahan, M. J., and Whitsett, J.A. Ontogeny of surfactant proteins A and B in human amniotic fluid as indices of fetal lung maturity. Pediatr Res 30(6), 597-605, 1991.

Whitsett, J.A., Clark, J.C., Wispe', J.R. and Pryhuber, G.S. Effects of TNF-α and Phorbol Ester on Human Surfactant Protein and MnSOD Gene Transcription In Vitro. Am J Physiol 262(6): L688-L693, 1992.

Whitsett, J.A., Pryhuber, G.S., Rice W.R., Warner B.B. and Wert, S.E. Acute respiratory disorders of the newborn. In: Neonatology, Pathophysiology and Management of the Newborn. Fourth Ed. G.B. Avery (ed). Lippencott Co., New York. p. 429-452, 1993.

Pryhuber, G.S., Church, S.L., Kroft, T., Panchal, A. and Whitsett, J.A. The 3' untranslated region of surfactant protein B mRNA mediates inhibitory effects of phorbol ester and tumor necrosis factor-α on SP-B expression, Am J Physiol 267(11): L16-L24, 1994.

Bachurski, C.J., Pryhuber, G.S., Glasser, S.W., Kelly, S.E. and Whitsett, J.A. Tumor Necrosis Factor-α inhibits surfactant protein-C gene transcription. J Biol Chem 270(33): 119402-19407, 1995.

Pryhuber, G.S., Bachurski, C.J., Hirsch, R., Bacon, A. and Whitsett, J.A. Tumor necrosis factor-α associated with decreased surfactant protein B mRNA expression in murine lung. Am J Physiol 14(5):L714-721, 1996.

O'Reilly, M.A., Stripp, B.R. and Pryhuber, G.S. Epithelial-mesenchymal interactions in the alteration of gene expression and morphology following lung injury. Micro Res Tech 38: 473-479, 1997.

Pryhuber, G.S., Khalak, R. and Zhao, Q. Regulation of surfactant proteins A and B by TNF-α and phorbol ester independent of NF□B Am J Physiol 274:L 289-L 295, 1998.

Pryhuber, G.S. Regulation and Function of Pulmonary Surfactant Protein B. Mol Gen Metab 64:217-228, 1998.

Whitsett, J.A., Pryhuber, G.S., Rice, W.R., Warner, B.B. and Wert, S.E. Acute respiratory disorders of the newborn; Meconium Aspiration, Persistent Pulmonary Hypertension. In: Neonatology: Pathophysiology and Management of the Newborn. Fifth ed., eds. Avery, G.B., Fletcher, M., MacDonald, M.G. Lippencott Co., New York. pg. 485-508, 1999.

Khalak, R., Huyck, H. and Pryhuber, G.S. Antagonistic Effects of Pyrrolidine Dithiocarbamate (PDTC) and N-Acetyl-l-Cysteine on Surfactant Protein Expression. Exp Lung Res, 25: 479-493, 1999.

Pryhuber, GS, Huyck, H. Induction of TNF Receptor Associated Factor 1 (TRAF-1) in Pulmonary Epithelial Cells by TNF-□ and Phorbol Ester. Am J Resp Cell Mol Biol , 22: 150-156, 2000.

Pryhuber, GS, O'Brien,D, Baggs, R, Phipps, R, Huyck, H, Peschon, J and Nahm, M. Role of the Type I Tumor Necrosis Factor Receptor (p55) in Oxygen Toxicity. Am J Physiol. 22: L1082-1090, 2000.

Uy, IP, Pryhuber, GS, Chess, PR, and Notter, RH. Combined-Modality Therapy with Inhaled Nitric Oxide and Exogenous Surfactant in Term Infants with Acute Respiratory Failure. Ped Crit Care, In Press, October, 2000.

O'Reilly, MA, Staversky, RJ, Huyck, HL, Watkins, RH, Baggs, RB, Maniscalco, WM, and Pryhuber, GS. p53-dependent and independent regulation of apoptotic genes during hyperoxic lung injury. Am J Physiol, In Review, 2000.

RECENT PERTINENT ABSTRACTS

Pryhuber , G.S. and Huyck, H.L.Induction of TNF Receptor Associated Factor 1 (TRAF1) in H441 Pulmonary Epithelial Cell Line, Human and Murine Lung. Am Rev Resp Dis , Presented: Poster Discussion, 1999.

Pryhuber, G.S., Huyck, H.L., Staversky, R.J. and O'Reilly, M.A. Anti-Apoptotic Pattern of Gene Expression in Mouse Lung Exposed to 100% Fio_2. Am Rev Resp Dis , Presented: Minisymposium, 1999.

O'Reilly, MA., Staversky, Huyck, HL and Pryhuber, GS. Regulation of BCL-2 Family Members in Mouse Lungs Exposed and Recovered From Hyperoxia by p53. Am Rev Resp Dis, 159(3):A172, 1999.

G. Pryhuber, H. Huyck And G. Reichlen. .Expression of TNF Receptor Associated Factors (TRAFs & cIAPs) in Human and Murine Pulmonary Epithelial Cells. Cytokine, 11(11): 930, 1999.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Robert A. Sinkin, M.D.	Associate Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Colgate University, Hamilton, NY	A.B.	1976	Chemistry
University of Rochester, Rochester, NY	M.D.	1980	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1980-1984	Intern, Junior, Senior, Chief Resident - Children's Hospital of Oakland, Oakland, CA
1984-1987	Fellow - Division of Neonatology, Department of Pediatrics, University of Rochester, Rochester, NY
1987-1988	Senior Instructor - Division of Neonatology, University of Rochester, Rochester, NY
1988-1994	Assistant Professor of Pediatrics (Neonatology) - University of Rochester, Rochester, NY
1990-1991	Assistant Director of Pediatrics; Director of Newborn Services, Highland Hospital, Rochester, NY
1991-	Medical Director, Neonatal Intensive Care Unit, Children's Hospital at Strong , Rochester, NY
1993-	Associate Chief, Clinical Affairs, Division of Neonatology
1994-	Associate Professor of Pediatrics (Neonatology) - University of Rochester, Rochester, NY

ACADEMIC HONORS

New York State Regents College Scholarship
Medal given by American Institute of Chemistry
Summa Cum Laude with High Honors in Chemistry
Edwin Foster Kingsbury Prize in Chemistry
Nathaniel B. Stanton Scholarship –Chemistry
Israel Scholar -Soroka Medical Center, Beer Sheva 1997
Phi Beta Kappa
Sisson Math Prize
Charles A. Dana Scholar
Buswell Fellow 1990
Society for Pediatric Research 1993
Best Doctors in America, 1998

REPRESENTATIVE PUBLICATIONS

Sinkin RA, Phelps DL. New strategies for the prevention of Bronchopulmonary Dysplasia. Clin Perinat 1987;14:599-620.

Sinkin RA, Shapiro DL. Surfactant replacement therapy. In: Bronchopulmonary Dysplasia (eds. E. Bancalari, JT. Stocker), Hemisphere Publishing Corp., Washington, D.C., 1988, p.345-355.

Kendig JW, **Sinkin RA**. The effect of surfactant replacement therapy on conditions associated with RDS: patent ductus arteriosus, intra-ventricular hemorrhage, and bronchopulmonary dysplasia. Sem perinat 1988;12:255-258.

Davis JM, **Sinkin RA**, Aranda JV. Drug therapy for bronchopulmonary dysplasia. Pediatric Pulmonology 1990;8:117-125.

Sinkin RA, Cox C, Phelps DL. Predicting risk for bronchopulmonary dysplasia: selection criteria for clinical trials. Pediatr 1990;86:728-736.

Sinkin RA, Davis JM. Cardiopulmonary resuscitation in the newborn. Pediatr in Review 1990;12:136-141.

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, **Sinkin RA**, Bartoletti A, Dweck HS, Horgan MJ, Risemberg H, Phelps DL, Shapiro DL. A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns less than 30 weeks gestation. N Eng J Med, 1991;324:865-871.

Finkelstein JN, Horowitz S, **Sinkin RA**, Ryan RM. Cellular and molecular responses to lung injury in relation to induction of tissue repair and fibrosis. Clin Perinat 1992; 19:603-620.

Sinkin RA, LoMonaco MB, Finkelstein JN, Watkins RH, Cox C, Horowitz S. Increased fibronectin mRNA in alveolar macrophages following *in vivo* hyperoxia. Amer J Resp Cell Mol Biol 1992;7:548-555.

Spafford PS, **Sinkin RA**, Cox C, Reubens L, Powell KR. Prevention of central venous catheter-related Staphylococcus species coagulase negative sepsis in neonates. J Pediatr 1994;125:259-263.

Sanders RJ, Cox C, Phelps DL, **Sinkin RA**. Two doses of early intravenous dexamethasone for the prevention of Bronchopulmonary dysplasia in babies with Respiratory Distress Syndrome. Pediatr Res 1994;36:122-128.

Maniscalco WM, **Sinkin RA**, Watkins RH, Campbell MH. Transforming growth factor-β1 modulates type II cell fibronectin and surfactant protein C expression. American Journal of Physiology: Lung Cell and Molecular Physiology 1994;267:L569-L577.

Sinkin RA, Sanders RJ, Horowitz S, Finkelstein JN, LoMonaco MB. Cell-specific expression of fibronectin in adult and developing rabbit lung. Pediatr Res 1995;37:189-195.

D'Angio CT, **Sinkin RA**, LoMonaco MB, Finkelstein JN. Interleukin-8 and monocyte chemoattractant protein-1 mRNAs in oxygen-injured rabbit lung. American Journal of Physiology: Lung Cell Mol Physiol 1995;12:L826-L831.

LoMonaco MB, Barber CM, **Sinkin RA**. Differential cytokine mRNA expression by neonatal pulmonary cells. Pediatric Research 1996;39:248-252.

Konno S, Numaguchi Y, Shrier DA, Qian J, **Sinkin RA**. Unusual manifestation of a vein of Galen malformation: value of CT angiography. Amer J Neurorad 1996;17:1423-1426.

Maniscalco WM, Watkins RH, Chess PR, **Sinkin RA**, Horowitz S, Toia L. Lung cell-specific expression of fibronectin and the EIIIA and EIIIB splice variants after oxygen injury. American Journal of Physiology: Lung Cell Mol Physiol 1998;18:L599-L609.

Sinkin RA, Kramer BM, Merzbach JL, Myers GJ, Brooks JG, Palumbo DR, Cox C, Kendig JW, Mercier CE, Phelps DL. School age follow-up of prophylactic versus rescue surfactant trial: pulmonary, neurodevelopmental and educational outcomes. Pediatrics 101(5)(electronic pages). http://www.pediatrics.org/cgi/content/full/101/5/e11.

Kendig JW, Ryan RM, **Sinkin RA**, Maniscalco WM, Notter RH, Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens L, Risemberg H, Phelps DL, for the Rochester Surfactant Trials Group. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics 1998;101(6):1006-1012, 1998.

Sinkin RA, Roberts M, LoMonaco MB, Sanders RJ, Metlay LA. Fibronectin expression in bronchopulmonary dysplasia. Pediatric and Developmental Pathology 1998;1:494-502.

Charafeddine L, Numaguchi Y, **Sinkin RA**. Disseminated coagulopathy associated with transtorcular embolization of vein of Galen aneurysm in a neonate. J Perinatology 1999;19:61-63.

Amin SB, **Sinkin RA**, McDermott MP, Kendig JW. Lipid intolerance in neonates receiving dexamethasone for bronchopulmonary dysplasia. Arch Pediatr Adol Med 1999;153:795-800.

Stevens TP, Hall CB, Maniscalco WM, **Sinkin RA**. Risk of RSV-associated hospitalization and economic impact of RSV prophylaxis for premature infants born ≤ 32 weeks gestation. Arch Pediatr Adolesc Med 2000;154:55-61.

Hall CB, Stevens TP, Swantz RJ, **Sinkin RA**, McBride JT. Development of Local Guidelines for Prevention of Respiratory Syncytial Virus Infections. J Pediatric Infectious Disease Journal 1999;18(10):850-3.

Sinkin RA, Dweck HS, Horgan MJ, Gallaher KJ, Cox C, Maniscalco WM, Chess PR, D'Angio CT, Guillet R, Kendig JW, Ryan RM, Phelps DL. Early dexamethasone – attempting to prevent chronic lung disease. Pediatrics 2000; 105:542-548.

D'Angio CT, Maniscalco WM, Ryan RM, Avissar NE, Basavegowda K, **Sinkin RA**. Vascular endothelial growth factor (VEGF) in pulmonary lavage fluid from premature infants: effects of age and postnatal dexamethasone. Biol Neonate. 1999 Nov;76(5):266-73.

The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), A Randomized, Controlled Trial. I: Primary Outcomes. Pediatrics 2000; 105: 295-310.

Relevant Abstracts

Maniscalco WM, **Sinkin RA**, Campbell MH, Watkins RH. TGF□$_1$ increases fibronectin mRNA and decreases SP-C mRNA levels in alveolar type II cells *in vivo*. Pediatr Res 35:395A, 1994.

Avissar NE, Johnston C, Ryan RM, Phelps DL, **Sinkin RA**, Finkelstein JN. Regulation of lung glutathione peroxidases by hyperoxia.Amer Rev Resp Crit Care Med 153:A734, 1996.

Basavegowda K, D'Angio CT, Finkelstein JN, **Sinkin RA**. Effect of early postnatal dexamethasone on IL-8 in human tracheal aspirate and deep pulmonary lavage. Pediatr Res 41:1463A, 1997.

Ryan RM, Myers GJ, Kendig JW, Cox C, Merzbach JL, Kramer BM, Palumbo DR, Phelps DL, **Sinkin RA**. School age neurodevelopmental outcome in surfactant-treated premature infants with and without chronic lung disease. Pediatr Res 41:1584A, 1997.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Timothy P. Stevens	Assistant Professor

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Brown University, Providence, Rhode Island	BS	1983	Biology
University of Rochester School of Medicine	MD	1987	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PREVIOUS EMPLOYMENT

1987-1990 Pediatric Residency (PL1-3) Strong Memorial Hospital, University of Rochester School of Medicine, Rochester, New York
1990-1991 Senior Chief Resident and Clinical Instructor in Pediatrics, Strong Memorial Hospital, Rochester, New York
1991-1994 Major, United States Air Force, Laughlin AFB, Texas Honorable Discharge
1994-1997 Instructor and Fellow in Neonatology, Strong Memorial Hospital, Rochester, New York
1997-1999 Clinical Assistant Professor of Pediatrics, State University of New York, Upstate Medical University, Syracuse, New York
1999-present Clinical Instructor of Pediatrics, Strong Memorial Hospital, University of Rochester, Rochester, NY

HONORS AND AWARDS

1991 National Defense Service Medal
1991 Air Force Training Ribbon
1991 Air Force Outstanding Unit Award
1995 Appointed to NIH Molecular Biology Training Grant,
University of Rochester, Rochester, NY
St. Joseph's Hospital, Syracuse NY
1998 Excellence in Teaching Award
Family Practice Residency Program, St. Joseph's Hospital, Syracuse NY
2000 Excellence in Teaching Award
Family Practice Residency Program

PUBLICATIONS

Stevens TP, McBride JT, Peake J, Pinkerton K, Stripp BR. Cell proliferation contributes to PNEC hyperplasia following acute airway injury in adult mice. Am J Physiol 272 (Lung Cell Mol Physiol 16): L486-L493, 1997.

Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. RSV-associated hospitalization and economic implications of RSV prophylaxis for premature infants born ≤ 32 weeks gestation. Arch Pediatr Adolesc Med. 2000;154:55-61.

LETTERS, EDITORIALS, SHORT ARTICLES, CASE REPORTS:

Stevens TP, Guillet R. "Use of Glucagon to Treat Low-Output Congestive Heart Failure Following Maternal Labetalol Therapy: A Case Report". J Pediatr 1995; 127(1):151-153.

Watson WJ, Stevens TP, Weinberg GA. "Profound anemia in an infant delivered to a mother receiving combination antiretroviral therapy for HIV infection". Pediatr Infect Dis J, 1998; 17(5):435-436.

Hall CB, Stevens TP, Swantz RJ, Sinkin RA, McBride JT. "Development of Local Guidelines for Prevention of Respiratory Syncytial Virus Infections" Pediatr Infect Dis J, 1999; 18(10):850-3.

ABSTRACTS PRESENTED AT NATIONAL/REGIONAL MEETINGS:

Stevens TP, McBride JT, Stripp BR. Increased calcitonin-gene related peptide (CGRP) expression in a model of acute airway injury in adult mice. Am J Respir Crit Care Med 1996; 153(4 Part 2): A725.

Stevens TP, Hall CB, Maniscalco WM, Sinkin RA. Risk of RSV-associated (RSV-hosp) hospitalization and economic impact of RSV prophylaxis for premature infants born $\leq$ 32 weeks gestation. Ped Res 1997; 41(4 Part 2): A227.

BIOGRAPHICAL SKETCH

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Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Robert J Swantz	Assistant Professor

EDUCATION (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
College of William and Mary, Williamsburg, VA	B.S.	1983	Biology
University of Virginia School of Medicine, Charlottesville, VA	M.D.	1987	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL AND TRAINING EXPERIENCE

1987-1990 Pediatric Internship and Residency at Strong Memorial Hospital, University of Rochester, Rochester, NY.

1990-1993 Fellowship in Neonatal-Perinatal Medicine at the Children's Hospital Medical Center, Cincinnati, Ohio

1993-1995 Senior Instructor, Division of Neonatology, Department of Pediatrics at the University of Rochester School of Medicine, Rochester, NY.

1995-pres Assistant Professor of Pediatrics, Division of Neonatology, Department of Pediatrics at the University of Rochester School of Medicine, Rochester, NY.

1993-1994 Assistant Medical Director, Neonatal Intensive Care Unit, Children's Hospital at Strong, Strong Memorial Hospital, University of Rochester, Rochester, NY.

1994-pres Associate Medical Director, Neonatal Intensive Care Unit, Children's Hospital at Strong, Strong Memorial Hospital University of Rochester, Rochester, NY.

1995- pres Associate Director of Pediatric Clerkship, Department of Pediatrics, University of Rochester School of Medicine and Dentistry, University of Rochester, Rochester, NY.

1997- pres Transport Medical Director, Neonatal Transport Team, Children's Hospital at Strong, Strong Memorial Hospital, University of Rochester, Rochester, NY.

HONORS

National Research Service Award, University of Cincinnati, Cincinnati, Ohio, 1992-1993.
Quality Achievement Award for Leadership in Neonatal Intensive Care Unit Quality Improvement, Strong Memorial Hospital, Rochester, New York, 1996.

PUBLICATIONS

Swantz R. Imaging strategies for neonatal pulmonary disease. Resident and Staff Physician, February supplement 17-21, 1993.

Korfhagen T, Swantz R, Wert S, McCarty J, Kerlakian C, Glasser S, Whitsett J. Respiratory epithelial cell expression of human transforming growth factor-alpha induces lung fibrosis in transgenic mice. Journal Clinical Investigation 93:1691-1699, 1994.

Hall CB, Stevens TP, Swantz RJ, Sinkin RA, McBride JT. Development of local guidelines for prevention of respiratory syncytial viral infections. Pediatric Infectious Diseases Journal 18(10): 850-853, 1999.

ABSTRACTS

Korfhagen T, Glasser S, Berhans M, Swantz R, Fink I, Wert S. Transforming growth factor-α affects tubule formation of explanted mouse embryonic lungs. Abstract presented at American Lung Association/American Thoracic Society International Conference, Miami, FL, May 1992.

Swantz R, Fink I,Wert S, Korfhagen T. Transforming growth factor-α remodels tubule formation of murine fetal lungs in culture. Abstract presented at the Sixth Annual North American Cystic Fibrosis Conference, Washington DC, October 1992.

Korfhagen T, Swantz R, McCarty J, Glasser S, Wert S, Whitsett J. Pulmonary fibrosis in transgenic mice bearing SP-C TGF-α chimeric genes. Abstract presented at the Sixth Annual North American Cystic Fibrosis Conference, Washington DC, October 1992.

Korfhagen T, Swantz R, McCarty J, Glasser S, Wert S, Whitsett J. Transgenic Mice Bearing SP-C TGF-α transgenes from fibrotic-like interstitial lesions. Abstract presented at the American Lung Association and American Thoracic Society International Conference, San Francisco, CA, May 1993.

Korfhagen T, Kerlakian C, Wert S, Whitsett J, Swantz R, Glasser S. Epithelial-mesenchymal interactions in the generation of pulmonary fibrosis in transgenic mice expressing TGF-α. Abstract presented at Seventh Annual North American Cystic Fibrosis Conference, Dallas, TX, October 1993.

Kerlakian C, Wert S, Bruno M, Swantz R, Glasser S, Whitsett J, Korfhagen T. Epidermal growth factor-receptor expression in fibrotic lesions of transgenic mice expressing TGF-α. Abstract presented at 1994 American Lung Association/American Thoracic Society Conference, Boston MA, May 1994.

Amin S, Watkins R, Swantz R, Staversky R, Maniscalco W. Expression of vascular endothelial growth factor (VEGF) and its receptor (flk-1) increase during lung development. Pediatr Res 39:A323, 1996.

Brooks AM, McBride JT, Barth R, McConnochie K, Swantz R, Szilagyi P. Contribution of prematurity to asthma burden in the first three years of life. Accepted for 1999 ALA/ATS International Conference, San Diego, CA, April 1999.

OTHER SUPPORT

PHELPS, D.L.

ACTIVE

U10 EY12471 Subcontract to Univ of Texas NEI Grant (Good) 7/1/00 - 6/30/02 %
NIH/NEI $12,000 estimate
ET-ROP: A Multicenter Trial of Early Treatment for ROP

The major goal of this project is to determine if treatment of high risk prethreshold ROP vs threshold ROP improves visual outcomes.

to be assigned Subcontract to Oregon Health Sciences (Palmer) 2000 - 2001 %
NIH/NEI Capitation Pending
CRYO-ROP: 15 year follow up

The major goal of this project is to determine 15 year outcomes after cryotherapy to one eye randomly selected at threshold ROP.

EY 09962-06 (Phelps) 5/1/93-4/30/01 %
NIH/NEI, current year $30,600
STOP-ROP: A Multicenter Trial of Oxygen for Prethreshold ROP

The major goal of this project is to test the hypothesis that supplemental oxygen can reduce the progression of moderate ROP to severe Retinopathy of Prematurity. Extension for manuscript writing.

U10 EY09959-05 (Phelps) 1/1/95-9/29/2000 %
NIH/NEI, current year $ no additional funds
Supplemental Therapeutic Oxygen in Prethreshold ROP (STOP-ROP) Participating Center

The major goal of this project is to test the hypothesis that supplemental oxygen can reduce the progression of moderate ROP to severe Retinopathy of Prematurity.

OVERLAP

There is scientific, but no effort overlap between these projects. There is no overlap with the current proposal.

RUEBENS, L.

ACTIVE

No Project Number (Chess) 4/1/98 - 10/1/00 %
Private Support $14,028
"New Mode of Ventilation for Premature Infants"

Premature infants are routinely exposed to assisted ventilation as a life saving intervention. The goal of this project is to investigate whether supporting each breath physiologically with assist-control ventilation will allow for more growth and healing, ultimately leading to earlier extubation and less chronic lung disease compared to standard synchronized intermittent mandatory ventilation.

M01-RR00044-39 (Goldsmith) 12/1/99 - 11/30/00 %
NIH $1,411,876 Variable
General Clinical Research Center

Research Nurse for multiple CRC approved clinical trials.

OVERLAP

There is potential overlap in science if the current proposal is funded. Budgetary overlap could occur depending on the number of protocols, but is unlikely. This will be carefully negotiated with the NICHD to adjust her effort appropriately.

WOODS, J.R.

ACTIVE

5T32 DA 07232 (Bidlack) 7/1/96 - 6/30/01 NA
NIH/NIDA $864,000
"Pharmacology of Drug Abuse Training Grant"

The major goal of this project is to support the training of three graduate students and two postdoctoral fellows to become highly competent scientists in the field of drug abuse.

PENDING

Pending Support

OVERLAP

No financial or scientific overlap.

MYERS, G.J.

ACTIVE

5 R01 ES08442 (Clarkson) 8/1/97 -1/31/01 %
NIH/DHHS/PHS $783,018
"Developmental Toxicity of Methyl Mercury"

The major goal of this project is to determine whether prenatal or postnatal exposure to methyl mercury from fish consumption adversely affects child development.

PENDING

Pending Support

The major goal of this project is to determine if dietary factors related to fish consumption influence the toxicity of low-dose exposure to methyl mercury.

OVERLAP

No significant overlap for funding or scientific objectives with the current proposal.

CHESS, P.R.

ACTIVE

HL03910-02 (Chess) 7/1/99 - 6/30/04 %
NIH/Mentored Clinical Scientist Development Award $116,995
"Cell Signaling of Mechanical Strain in Pulmonary Epithelia"

The purpose of this grant is to investigate the mechanisms involved in strain-induced proliferation in the lung at a cellular level. By better understanding how strain affects the lung, we can optimize beneficial strain effects and mitigate detrimental ones.

No Number Assigned (Chess) 4/1/98-10/1/00 %
Private Support $14,028
"New Mode of Ventilation for Premature Infants"

Premature infants are routinely exposed to assisted ventilation as a life saving intervention. The goal of this project is to investigate whether supporting each breath physiologically with assist-control ventilation will allow for more growth and healing, ultimately leading to earlier extubation and less chronic lung disease compared to standard synchronized intermittent mandatory ventilation.

R01 HL56002 (Phipps) 9/1/97 - 8/31/02 %
NIH $131,689
"Role of CD40 in Lung Inflammation and Fibrosis"

This grant investigates the role of CD40-CD40 receptor cell-signaling pathways on inflammation in the lung.

OVERLAP

There is no scientific or funding overlap with the current proposal.

D'ANGIO, C.T.

ACTIVE

K08-HL03493-02 (D'Angio) 7/1/97 – 6/30/02 %
NIH/NHLBI $77,410
Chemokine Regulation in Pulmonary Oxygen Injury

This grant centers on the basic mechanisms of chemokine regulation underlying the development of pulmonary inflammation and eventual fibrosis in the newborn.

% = Percentage of Effort

N01-AI-45248 (Treanor) 9/30/94 – 9/29/01 %
NIH/NIAID $1,405,934
"Evaluation of Control Measures Against Infectious Diseases Other than AIDS"

The goal of this project is the evaluation of vaccines and vaccine immunology in orphan populations.

PENDING

Pending Support

OVERLAP

There would be a scientific overlap between K08-HL03493-02 and the pending Pending Support Project, and a potential overlap in funding. If both awards are received, effort will be adjusted to ensure no overlap.

GUILLET, R.

ACTIVE

No Number Assigned (Guillet) 7/99 - 12/02 %
Private Support $7,500 estimate
"Brain cooling for the treatment of perinatal hypoxic-ischemic encephalopathy"

To determine whether treatment of moderate to severe hypoxic-ischemic encephalopathy in term infants with head cooling and mild systemic hypothermia can produce meaningful improvements in neurodevelopmental outcome and survival rates at 18 months of age.

No Number Assigned (Guillet) 7/00 - 6/01 %
Private Support $3,000
"Brainstem maturation and feedings in preterm infants"

To determine if the addition of DHA to standard formula will increase the rate of maturation of the auditory brainstem evoked response in formula fed infants to that seen in infants who are fed breast milk.

No Number Assigned (Guillet) 7/00 - 6/01 %
Center for Mental Retardation and Developmental Defects $10,000
"Brainstem maturation and feeding in preterm infants"

To determine if the addition of DHA to standard formula will increase the rate of maturation of the auditory brainstem evoked response in formula fed infants to that seen in infants who are fed breast milk.

PENDING

Pending Support

The major goals of this project are to investigate the potential of antioxidant therapy in the prevention of premature rupture of membranes.

OVERLAP

There is 100% scientific overlap for the Private Support and Center for Mental Retardation and Developmental Defects grants. The Mead Johnson costs are for a research nurse. The Mental Retardation costs are for audiology. There is no financial or scientific overlap with current proposal.

LAROIA, N.

ACTIVE

No Number Assigned (Guillet) 7/99 - 12/02 %
Private Support $7,500 estimate
"Brain cooling for the treatment of perinatal hypoxic-ischemic encephalopathy"

The major goal of this project is to determine whether treatment of moderate to severe hypoxic-ischemic encephalopathy in term infants with head cooling and mild systemic hypothermia can produce meaningful improvements in neurodevelopmental outcome and survival rates at 18 months of age.

OVERLAP

There is no overlap with the current proposal.

MANISCALCO, W.M.

ACTIVE

U01 HL63400 (Maniscalco) 6/1/99 - 5/31/04 %
NIH/NHLBI Total Costs: $877,046
"Vascular Endothelial Growth Factor in Experimental BPD"

The major goal of this project is to evaluate microvascular development in non-human primate lung comparing normal to the chronic lung injury model of BPD.

OVERLAP

No financial or scientific overlap with this proposal.

PRYHUBER, G.S.

PENDING

Pending Support

Number pages consecutively at the bottom throughout the application. Do *not* use suffixes such as 3a, 3b.

% = Percentage of Effort

OVERLAP

None with the current proposal.

SINKIN, R.A.

ACTIVE

No Number Assigned (Glantz) 4/1/00 - 3/31/01 %
NYS Department of Health Contract $140,000
"Statewide Perinatal Data System – Finger Lakes Region" (co-Director)

The overall goal of this project is to enhance quality improvement activities with standardization and management of clinically based data on mothers and infants throughout New York State.

PENDING SUPPORT

Pending Support

Pending Support

OVERLAP

None

STEVENS, T.P.

ACTIVE

None

SWANTZ, R.J.

ACTIVE

None

% = Percentage of Effort

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory: A blood gas and electrolyte lab is located within the NICU continuously staffed by respiratory therapy and the clinical laboratories of the Strong Memorial Hospital are fully staffed around the clock. The main Neonatology research laboratories consist of 5500 square feet of interdisciplinary labs in the same building, facilitating collaborative work.

Clinical: The 52 bed NICU is a regional facility for the 11-county Finger Lakes area of Upstate New York which has 16,000 births/year regionally. Renovated in 1994, the state-of-the art NICU admits ~1200 infants/year and is able to provide conventional ventilation (Siemens, VIP Bird), high frequency ventilation (oscillatory or Jet),

Animal: inhaled NO, and ECMO. Approximately 50% of admissions are premature, and 170 <1500grams birth weight. The infants are cared for by 10 full time neonatal faculty, 6 fellows, nurse practitioners, housestaff, and excellent nurses and respiratory therapists. All labor,delivery, and Cesarean sections take place on the same 3rd floor as the NICU. Strong Memorial Hospital. Pediatrics is on the 4th floor.

Computer: Each faculty member and the research nurse has a Pentium (advanced) computer attached via ethernet to the University high speed connection to the library, clinical systems, internet and additional resources. Software for word processing, data analysis, reference tracking, graphics, e-mail, shared calendars, and presentation preparation is all available, as are laserjet printers and FAX. Backup is provided nightly by the University Server.

Office: Each faculty member has an office on the 4th floor of the medical center, and shares the support of four secretaries and 2.5 medical documentation clerks. Our research nurse shares a 300 square foot office on the 3rd floor, contiguous with the NICU.

Other: The Neonatal Continuing Care Clinic offices are approximately 220 square feet located on the 4th floor of the Ambulatory Care Building, contiguous to and attached to the main hospital building. 4-6 patient examining rooms are used as needed for the clinic held each Thurs. there.

The NIH General Clinical Research Center is located on the 4th floor of the hospital and is a valued resource for nursing support of research projects, statistical support in the design and monitoring of research projects and educational resources for trainees. The basic core laboratories assist in sample processing from research subjects in the NICU, and would be able to participate in projects requiring research laboratory support. Over the past 15 years, a portion of our research nurse's time has been funded in some years. The GCRC has unique environmental chambers/rooms that permit controlled exposures to gases and particles to adult humans over prolonged periods.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Equipment needed for clinical care of infants in the NICU is addressed in the body of the application. As a special resource, however, it is worth noting that the Aab Institute for Medical Research at the University of Rochester Medical Center is a newly opened (1999) state of the art facility for basic science and translational research. Core facilities include the transgenic and knock-out mouse vivarium, confocal microscopy, peptide sequencing core, oligoprobe preparation core, electron microscopy, and the many laboratories of the individual, internationally known investigators. Should protocols arise that require the collaboration of such scientists, Rochester has a long standing institutional tradition of co-operative ventures and shared research. These investigators and facilities would be an available resource.

NICHD Cooperative Multicenter Neonatal Research Network

The University of Rochester Medical Center's Division of Neonatology is ideally positioned to become a NICHD Neonatal Research Network Center under the direction of Dale L. Phelps, MD, a practicing Neonatologist and Professor of Pediatrics and Ophthalmology. She has 26 years of experience and leadership in multicenter neonatal clinical trials, bridging the laboratory to the Newborn Intensive Care Unit(NICU), and is prepared to commit herself to the Network's mission. Many of the Division's faculty are also trialists, experienced in designing, conducting and publishing multicenter randomized trials. The Rochester Region has a diverse population, and all high risk mothers and infants from a large, six county geographic region are served with a smoothly functioning referral system. Finally, the Neonatal Follow up Program has an enviable published success in follow up of enrolled research subjects, ensuring the completion of protocols.

1. Academic Productivity: Recent Experience in Clinical Research for the Division of Neonatology

The PI applicant and Division of Neonatology faculty have an active clinical research program coordinated with Maternal-Fetal Medicine and other University entities through their Clinical Trials Group (see section 9). Starting with the most recent, published clinical research for the past 5 years is described succinctly below, followed by more detailed enrollment information and faculty involvement in a recent example of a randomized controlled trial (RCT), and of an observational study.

A. Roles of the PI and other Faculty in recently published clinical research.
(* Authors who remain Rochester Faculty and would be Network Co-investigators are indicated by *)

- Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a Randomized Controlled Trial. I: Primary Outcomes. Pediatrics 105:295-310, 2000.(1) *Phelps was PI of this 30 center, RCT that enrolled 649. She wrote the proposal, designed the study with the Executive Committee, and chaired the Writing Committee that performed the analyses and wrote the manuscript.
- *Sinkin RA, Dweck HS, Horgan MJ, Gallaher, KJ, *Cox C, *Maniscalco WM, *Chess PR, *D'Angio CT, *Guillet R, Kendig JW, Ryan RA, *Phelps DL. Early dexamethasone: attempting to prevent chronic lung disease. Pediatrics 2000,105:542-548.(2) Sinkin was PI of this 4 center RCT. He wrote the proposal, designed the study with the assistance of co-authors at Rochester, and chaired the committee that worked on analyses with Cox, and wrote the manuscript. He performed site visits and data audits.
- *D'Angio CT, *Maniscalco WM, Ryan RM, Avissar NE, Basavegowda KP, *Sinkin RA. Vascular endothelial growth factor in pulmonary lavage fluid from premature infants: effects of age and postnatal dexamethasone. Biol Neonate 1999; 76:266-273.(3) This observational study was on pulmonary samples obtained from selected infants enrolled in the study above.(2) The co-authors were all from Rochester and participated in obtaining samples, analyses and writing of the manuscript.
- Amin, SB, Orlando MS, *Dalzell LE, Merle KS, *Guillet, R. Morphological changes in serial auditory brainstem responses (ABRs) in 24-32 weeks' gestational age infants during the first week of life. Ear and Hearing, 20:410-418, 1999.(4) Guillet and Dalzell were the Sr. authors on this observational study conducted prospectively with Amin as fellow. Dalzell, audiologist and Guillet mentor faculty.
- Kendig JW, Ryan RM, *Sinkin RA, *Maniscalco WM, *Notter RH, *Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens LJ, Risemberg H, *Phelps D. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics 101:1006-1012, 1998.(5) Kendig was the PI of this 3 center RCT from the Rochester investigators who designed the

study. Kendig chaired analysis and writing committee that we all worked on. Dr. Kendig is now at Hershey.

- *Sinkin RA, Kramer BM, Merzbach JL, *Myers GJ, Brooks JG, Palumbo DR, Cox C, Kendig JW, *Phelps DL. School age follow-up of prophylactic versus rescue surfactant trial: pulmonary, neuro-developmental and educational outcomes. *Pediatrics*, 1998;101(5). URL: http://www.pediatrics.org/cgi/content/full/101/5/e11. (6) A Follow up study of the RCT enrollees. All 154 enrolled surviving infants from the Rochester center were located at school age--families of 148 (96%) consented to be evaluated. The children were located and evaluated by the Neonatal Follow up Program.
- Butler-O'Hara M, LeMoine C and *Guillet R. Analgesia for neonatal circumcision: A randomized controlled trial of EMLA cream vs. dorsal penile nerve block. Pediatrics, 101: electronic pages, 1998.(7) A single center RCT conceived by two of our Nurse Practitioners, design assistance, substantial input of Guillet.
- Khalak R, Pichichero ME, *D'Angio CT. Three year follow-up of vaccine response in extremely premature infants. Pediatr 1998; 101:597-603.(8) D'Angio as the lead author worked with a Neonatology fellow, Khalak, and the Follow up Program to continue observations of an original prospective observation study (see below 1995(9)). 100% follow up strengthened the results of this single center project.
- *Laroia, N., *Guillet, R., Burchfiel, J. and McBride M.C. EEG background as predictor of electrographic seizures in high-risk neonates. Epilepsia, 39:545-551,1998.(10) Laroia and Guillet were active members of the Rochester collaborative group that performed this challenging prospective observational study involving 24 hour recordings of EEG with simultaneous video on neonatal seizures. The collaboration of the Comprehensive Epilepsy Center made this feasible with 24 hour a day technical support. The long term follow up of these infants has recently been completed with the help of the Follow up Program (results in press, 10a).
- Hudak ML, the Infasurf *v* Exosurf Study Group (W *Maniscalco, PI for Univ of Rochester). Infasurf *vs* Exosurf for the treatment of neonatal respiratory distress syndrome: a multicenter randomized masked comparison trial. J Pediatr 1996;128:396-406.(11) A RCT designed and conducted in 21 centers by Hudak, PI. Rochester was a participating center, and Maniscalco PI locally. He participated in the data analysis and writing of the manuscript which enrolled 66 infants from Rochester, 1,133 infants total. Since this protocol was monitored by the FDA, the investigators and our research nurse, Linda Reubens, became skilled and familiar with their audit process.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity: Snellen visual acuity and structural outcome at 5½ years after randomization. Arch Ophthalmol 1996;114:417-424.(12) Phelps is on the Permanent Executive and Editorial Committees. The 5½ year follow up of surviving infants enrolled in the original CRYO-ROP RCT. Phelps is PI of the Upstate NY center (1 of 23) and contributed follow up on 18 of the surviving 19 infants from our center. She also contributed substantively to the data analysis and writing of this manuscript.
- *D'Angio CT, *Maniscalco WM, Pichichero ME. Immunologic response of extremely premature infants to Tetanus, *Haemophilus influenzae* and Polio immunizations. Pediatrics 1995;96:18-22.(9) An observational study of 23 infants from Rochester, designed, conducted and written jointly by the co-authors.
- Wagner CL, Kramer BM, Kendig JW, Brooks JG, Cox C, Wagner MT, *Phelps DL. School-Age follow-up of a single-dose prophylactic surfactant cohort. J Dev Behav Pediatrics 1995;16:327-332.(13) Wagner, a fellow in Neonatology, interviewed the patients and reported long term follow up of a RCT with the assistance of the Follow up Program who assisted in locating the children, and evaluating them. This important small population included the infants enrolled in the first RCT of placebo vs surfactant. 40 of 43 survivors were located (93%), and 39/43 (91%) consented to full follow up evaluation.

These past five years are the most "recent", but the preceding years contributed greatly to our maturity as an investigative group. We designed and ran many of the seminal surfactant trials (a single center RCT of single dose saline placebo vs surfactant given prophylactically in the delivery room(14), a 3-center RCT of multi-dose surfactant given prophylactically at birth vs rescue for RDS(15), and a 4-center RCT of immediate prophylatic vs post-stabilization prophylactic surfactant given in the delivery room(5)). During this time, we also entered the 23-center RCT of Cryotherapy for severe Retinopathy of Prematurity with Phelps on the Executive Committee.(16-21)

B. Roles and Performance in a Recent Multicenter Randomized Controlled Trial

The STOP-ROP study is a recent example of our center's participation in a multicenter randomized controlled trial. Dale Phelps, PI of the current proposal, was the PI of the Scientific Headquarters for this trial. She developed the concept, conducted the preparatory studies in animal models and worked with her colleagues on the Executive Committee to design, secure funding for, and run the trial. The EMMES Corporation was the Coordinating Center, and 30 centers participated over 6 years of enrollment. It was supported by the NEI, NINR, and 10 of the NICHD Neonatal Research Network centers participated. Dr. Phelps was Chair of the Permanent Executive Committee and chaired the Writing Committee that analyzed the data and wrote the final manuscript.(1)

Rochester was one of the participating centers (a consortium including Buffalo Children's Hospital), with Phelps as PI. Predicted enrollment was 7/yr, and over the 5 year 1 month study, 34 were enrolled (6.68/12 months). Study logs demonstrate 68 infants had prethreshold ROP, 39 met eligibility criteria, and of those, 34 (87%) were enrolled, the reason for non-enrollment being parent refusal. The gender and ethnicity distributions for our Center's enrollees, as well as the entire study, are shown in Table 1.

Table 1: STOP-ROP Enrollment, Gender, Ethnicity

	Rochester Center	Full STOP-ROP Cohort
enrolled and randomized, n	34	649
male n (%)	23 (67%)	371 (57%)
Caucasian, n (%)	20 (59%)	359 (55%)
Black, n (%)	13(38%)	192 (30%)
Hispanic, n (%)	0 (%)	57 (9%)
other, n (%)	1 (3%)	41 (6%)

C. Roles and Performance in a Recent Observational Study

The immunologic responses of extremely premature infants to tetanus, *Haemophilus influenzae* and polio immunizations(9) is a small observational study conducted in one center, but that demonstrates the ability of the Follow Up Program to facilitate very high rates of protocol completion. During the year of enrollment, 25 infants were eligible (<29 weeks gestation, <1.0kg birth weight, alive at 2 months in the hospital, lived within the referral area, and no ongoing sepsis or immunodeficiency disease). Families of 23 consented to the prospective collection of blood samples following vaccinations at 2 months. Thereafter, 1 infant died, 1 family withdrew consent, 4 failed to complete vaccine administration within the study time window, and one blood sample was missed. Thus 16 infants completed the first phase of the study. Their gender and ethnic distribution are shown below in Table 2 for Phase I, and it was observed that eligible non-white families were less likely to accept the study.

Blood samples were obtained before the 2 month vaccines and 4-6 weeks after the 6 month vaccines. Values were compared to a larger set of available samples from full term infants gathered in the same geographic region following the same vaccinations.

Table 2: Vaccine Immunogenicity Study Enrollment

	Eligible– Did complete Study (n=16)	Eligible-- Did not Complete (n=7)
No Consent/withdrew	0	2
Female (%)	8 (50%)	5 (71%)
Non-white (one mixed)	8 (50%)	7 (100%)

Three years later, these same 16 infants were sought out for a follow up study not originally planned.(8) Also 17 full term infants were recruited from the pediatric clinic matched on age, and immunization status (complete). All 16 of the original infants were located and agreed to return for blood sampling between 3 and 4 years of age, before the series of booster vaccines began. Demographics of the study infants and the recruited comparison group are shown below as published. (The change in non-white status of 1 study infant is because of reclassification of a mixed heritage infant)

Table 3: Vaccine Immunogenicity Study Follow up at 3 years

	Original Study (n=16)	Comparison Full Term Infants recruited (n=17)
Female (%)	8 (50%)	8 (47%)
Non-white	7 (44%)	15 (88%)
Medicaid	5 (31%)	17 (100%)

At seven years, the immune status of these infants was once again evaluated (data not yet in press, provided courtesy of D'Angio). With the heroic efforts of our Follow up Program Staff, all 16 of the premature infants, and 16 of the 17 full term infants from the second phase were located. All 16 premature infants agreed to return for blood samples, but 7 of the full term 7 year olds refused and were replaced with matched controls. The ability to locate and obtain consent from the NICU graduates speaks to the loyalty of our patients, the dedication of the Follow up staff and their ability to engender that loyalty. This is not unusual in Upstate New York, and is a major strength of our center's ability to complete follow up.

D. Generic Database (GDB) Eligible Infants over the Past 5 Year

Rochester has not been a Network Center, but we provide the number of inborn, live births of 400-1500 grams birth weight that would have been eligible for the GDB, plus the comparable transports.

Table 4: FiveYear History of Rochester Infants Eligible for the GDB

Year	Live Births 400-1500g **	Admitted to NICU 400-1500g ♮	Transports 400-1500g	Total GDB infants 400-1500g
1995	148	136	19	167
1996	140	137	26	166
1997	142	130	10	152
1998	162	156	29	191
1999	146	153	17	170

** Note that the difference between infants live born per the Perinatal database and the number of those admitted to the NICU represent infants that expired in the delivery room, plus...

♮ A second source of discrepancy is that the Neonatal Database considered an infant born in the emergency room of Strong Memorial Hospital an "inborn" infant, while the Perinatal Database treats these infants as "outborn". When performing a search, this discrepancy is easily corrected since the actual place of birth is coded in both the Perinatal and Neonatal data bases.

2. Neonatology Staffing: Faculty of the Division of Neonatology

A. Neonatology Divisional Organization as an Academic Unit:

The Division of Neonatology includes 10 board certified neonatologists who care for the NICU infants (facilities described in section 5), Ruth Lawrence, MD who heads the Normal Newborn Nurseries and is one of the world's leading authorities on the medical aspects of Breast Feeding,(22) and Gary Myers, MD who leads the High Risk Follow up Clinic and is board certified in both Neonatology and Pediatric Neurology. Three full time research PhD faculty are also members of the Division and invaluable additions to our total research effort which involves a large laboratory based program looking at pulmonary oxygen toxicity and developmental lung injury, in addition to the clinical research. One to three fellows are recruited each year to our accredited Fellowship training program, learning the care of infants and the principals and skills needed in both basic and clinical research.

All faculty have 40-80% protected time for research, being responsible for attending for 10-18 weeks of the year (depends on mentored training award and extramural funding). Care is provided to the patients through a classic academic supervised system of Faculty--Fellow--Resident. Mid-level providers (Master's prepared Nurse Practitioners and Physician Assistants) work with the Faculty and Fellows to reduce the patient load for the residents and ensure full compliance with the Residence Review Committee limitations on NICU rotations and hours of call.

Weekly Fellow's conferences are led by the fellows and address critical evaluation of the literature, quality assurance questions, morbidity review and case presentations. Newly proposed research projects are typically presented for debate at these meetings. Weekly topic lectures provide didactic teaching of the fellows on a broad range of research, clinical, ethical and analytic skills. A weekly research seminar is held jointly with the Divisions of Adult Pulmonary Medicine and Department of Environmental Health and Toxicity at which faculty and fellows present their research annually, with several invited outside speakers.

The Division of Neonatology research program relates to those of the Department of Pediatrics, the Division of Maternal-Fetal Medicine and to the new Aab Research Center. This newly built state of the art facility is rapidly recruiting new faculty in six focused areas (Aging and Developmental Biology, Human Genetics and Molecular Pediatrics, Cancer Biology, Vaccine Biology and Immunology, Cardiovascular Biology, and Oral Biology). This extraordinary source of basic science, plus the bench research in our own Division will be the source of many future interventions to be brought to the Network for clinical trials.

B. Principal Investigator training, experience and publications – Dale L. Phelps, MD

PI: Dale Phelps, MD received her MD at Northwestern University Medical Center and trained as a Pediatrician at Children's Hospital in Chicago, Ill. Her Neonatology fellowship was with William Oh at Harbor General Hospital in Torrance, CA, and she then joined the Neonatology Faculty at UCLA in Westwood, CA. for 10 years. Although her fellowship training was mostly in metabolism, she turned to Retinopathy of Prematurity upon leaving her fellowship with enthusiasm to solve this problem through both laboratory and clinical research. She received initial R01 funding from the NEI for lab investigations that directly led to her first proposed Clinical Trial. A planning grant was awarded to develop the clinical trial proposal and it was then that she began to learn advanced clinical trials methodologies from biostatisticians who have been collaborators since, starting with Jacqueline Benedetti, PhD at UCLA who successfully helped her compete for her first R01 funded two-center trial of Vitamin E to prevent ROP which was completed with the help of Fredrick Dorey, PhD.(23,24)

As she moved to Rochester in 1984, she had just begun a collaboration with the group that was putting together the CRYO-ROP study with Earl Palmer, MD as PI. Dr. Palmer and Robert Hardy, PhD at the University of Texas School of Public Health became her next colleague/mentors, and as she provided

Neonatology consultation to that study, as well as ROP expertise, she also gained first hand experience on how to develop a multi-disciplinary protocol and run a 23 center RCT and Observational Study(12,16-21). The follow up in that trial continues (15 year follow up has just been funded.)

Anne Lindblad, PhD and Neal Oden, PhD at the EMMES Corporation became her collaborators in clinical trials as the basic lab research she had been working on with NEI funding finally came to maturity, ready for testing of supplemental oxygen for prethreshold ROP. That work was funded in 1993, completed enrollment in 30 centers in March 1999, and the results were published in Feb. 2000 after an accelerated data analysis and tremendous effort on the part of Dr. Phelps and her writing committee.(1)

Special recognition is also due William Silverman, MD who has been an invaluable mentor, pen pal and friend since 1976. In addition, John C. Sinclair, MD has been a mentor in the search for evidence based medicine, and accepted her for a formal sabbatical year studying Clinical Evaluative Sciences in 1997. At that time he also recruited her as a reviewer for the Neonatal Review Group of the Cochrane Library, and she has completed three of those reviews.(25-27)

Dr. Phelps has also gained experience outside of ROP as 1) a grant reviewer, 2) service on Data Safety and Monitoring Committees, and 3) as a collaborator and PI on non-ROP controlled trials with her colleagues in Rochester.

- From 1993-1997 she served on an NICHD Advisory Committee that reviewed grant submissions, many of which were clinical trials. Since then she has served on three Special Emphasis Review panels, reviewing grants for NEI, NICHD, and NHLBI.
- From 1994-98 she served as the Chair of the Data Safety Monitoring Board(DSMB) for NHLBI overseeing a muti-center trial of inhaled Beclovent to prevent BPD. From 1995-98 she served on the DSMB for the LIGHT-ROP study for the NEI. Since 1997, again for NEI, she has been on the DSMB that monitors the Pediatric Eye Disease Investigator's Group (PEDIG) -- Ophthalmologists in practice that have banded together to participate in multiple large simple clinical trials to address common questions where there are little or no data as to best practice. This group has a unique organization, with NEI funding of the Coordinating Center and DSMB. This has been an invaluable experience for Dr. Phelps in learning about additional practical approaches to excellent clinical research.
- After moving to Rochester in 1984, she worked with the Division investigators starting clinical trials of surfactant and helped to lead those efforts as the early trials progressed to the clinical project in a 10 year SCOR funded by NHLBI. Dr. Phelps was the PI of the clinical project in that SCOR, and many publications have resulted from those randomized controlled trials, each of which has served to expand her experience and knowledge.(5,6,13-15,28) The surfactant interventions took place in a New York state multicenter group that the SCOR grant managed. Data coordination was monitored, analyzed and managed at Rochester under the direction of the investigators, Dr. Phelps and Christopher Cox, PhD, biostatistician. Later during the SCOR funding, research realigned its focus towards the prevention of BPD with both clinical trials(2,29) and observational studies(30,31) to increase understanding of BPD and how to best select infants for future study.

Dr. Phelps assumed the responsibility of Division Chief in 1989 when Donald Shapiro, MD unexpectedly passed away. After 11 years, she is stepping down from this position to devote herself more fully to her research, and William Maniscalco, MD will take up that role. Phelps and Maniscalco have worked together collaboratively for the past 16 years, are both active members of the Rochester Clinical Trials Group (see section 9) and Maniscalco is fully supportive of this Application (letter attached). Dr. Phelps is eager for the opportunity to work with the Neonatal Research Network Investigators on the future for improved, evidence based neonatal care, and is grateful to have the increased time to do so with a supportive Division.

C. Individual Neonatology Faculty training, experience and publications

The following descriptions provide a supplemental narrative highlighting the key elements of each individuals' contributions to our Clinical Research Program. The Biosketch pages provide additional detail and many publications in addition to those listed here.

William Maniscalco, MD Professor of Pediatrics - Dr. Maniscalco received his medical degree from Johns Hopkins, and trained in Pediatrics at Children's Hospital, Boston. His Neonatology training was at Yale University with Ian Gross, and he was recruited with Donald Shapiro to come to Rochester in 1978 by David Smith. His primary research career has been lab based and R01 funded, largely from NICHD. However, Dr. Maniscalco has also been a strong contributing member of the division's Clinical Trials Group and was the principal investigator for the Infasurf vs. Exosurf multicenter collaborative study.(11) He has made substantive contributions to each of the many multicenter trials. (2,5,11,14,15), and connected these to the bench work of his primary funding.(3,32) He is extremely supportive of our Network Participation.

Robert Sinkin, MD Associate Professor of Pediatrics; Associate Division Chief for Clinical Affairs, Neonatology. Dr. Sinkin completed medical school at Rochester and his Pediatric training in Oakland. He completed fellowship training at the University of Rochester with Don Shapiro and was particularly recognized for his aptitude in clinical trials. After recruitment to the faculty, his first clinical project with Dr. Phelps led to a better way to identify infants at highest risk for BPD to recruit into prophylactic trials(30). He has led the early dexamethasone studies, from the pilot study done with a fellow(29), to the multicenter RCT that followed,(2) and currently is planning the school age follow up on those infants. Dr. Sinkin is an active participant in the Clinical Trials Group in the Division of Neonatology. His goal is to conduct trials aimed at reducing the morbidity associated with the respiratory distress syndromes of premature and term infants. As Medical Director of the Neonatal Intensive Care Unit he has direct responsibility for equipment and ancillary services within the Unit, and maintains communication with Nursing Management and Respiratory Therapy.

Ronnie Guillet, MD, PhD Associate Professor of Pediatrics - Dr. Guillet is the Chief of Pediatrics at Highland Hospital, a Level I community hospital in Rochester, and also the Director of the Neonatology Fellowship Program. She completed her medical degree and PhD in Biophysics at the University of Rochester, her Pediatric training with Roberta Ballard in San Francisco, and her Fellowship with Maria DelavoriaPapadopolus, MD at the University of Pennsylvania. When she joined the Rochester faculty, her special ability to teach science and guide Fellows made her a natural leader for our Fellowship Program. She has guided several fellows through excellent clinical projects (4,10,33,) and is a consistent, insightful contributor to the Clinical Trials Group and their publications.(2,5) She has instigated several interesting protocols with fellows or colleagues, and is skilled in pursuing them to conclusion.(7,35). Together with Dr. Laroia as co-PI, Rochester is a center in the multicenter International Trial of Head Cooling for perinatal asphyxia. To date, they have randomized 5 infants into that trial. She no longer has the protected time of a junior faculty member, but joins the ranks of the Senior faculty who are partially protected at [%] time.

Carl D'Angio, MD Assistant Professor of Pediatrics in Neonatology - Dr. D'Angio received his MD from Johns Hopkins University and did his Pediatric training at the University of Pennsylvania. Following a valuable experience at the Indian Health Service at Ft. Defiance where he began a lifelong, grant funded interest in vaccines,(8,9,36) he was accepted by the University of Rochester for neonatology training with Don Shapiro/Phelps, and recruited to the faculty in 1994, pursuing investigations in the inflammatory responses of the lung during development and injury with his goals set on understanding and controlling BPD. His basic science research is a tool, to be used for bridging laboratory findings to clinical therapy, and his academic role is being developed by the Division as our Translational Researcher. His time is protected

at [%] as a funded Jr. Faculty member who has a Career Development Award from NHLBI.

Robert Swantz, MD Assistant Professor of Pediatrics in Neonatology - Dr. Swantz is the Associate Medical Director of the NICU. He completed his MD at the University of Virgina, his Pediatric training in Rochester, and his Fellowship training at the University of Cincinnati with Tom Korfhagen. He joined the faculty in Rochester in 1993 and has assumed major responsibilities in the educational programs of the Medical Students in Pediatrics, and directs the Neonatal Nurse Transport System training and supervising the nurses in that role. He is supportive of controlled trials in the NICU, is an excellent and valued critic and runs the division statistics and quality assurance programs.

Nirupama Laroia, MD completed her Pediatric training in India and England, studying Neonatology at the Hammersmith Hospital in London. She came to the United States and completed required additional Pediatric training at the Medical College of Virginia, and completed her Fellowship in Rochester. She joined the Rochester faculty in 1998, and is the Director of our affiliated NICU at the Level II Rochester General Hospital in town, staffed by our Neonatal Faculty. It serves as an important step down unit for our very busy Level III Regional Center, and there is obviously excellent medical communication between the two units. Follow up for clinical trials is seamless from Strong Memorial Hospital(SMH) to Rochester General Hospital, and protocols are approved by the IRB of both institutions if there is the possibility of transfer before a study is complete. Infants who were in a research protocol at SMH are followed by our research nurse and Follow up Program if they are returned to the community hospital before the study is completed. That has been no difficulty in our trials. Dr. Laroia's research interest is in seizures(10,35) and Neuroprotection, and together with Dr. Guillet is a co-PI on the multicenter International Trial of head cooling for perinatal asphyxia. To date, they have randomized 5 infants into that trial.

Patricia Chess, MD Assistant Professor of Pediatrics in Neonatology. Dr. Chess joined the faculty in 1994 after completing her Residency and Fellowship training at the University of Rochester, having previously received her MD from Columbia University. Dr. Chess is studying signal transduction in type II cells and the effects of mechanical stain on the growth and injury response of epithelial cells. Her devotion to the effects of stretch/strain on the pulmonary epithelium come from her desire to control or prevent BPD in the NICU. She maintains an avid and valued interest in the NICU and the Clinical Trials group,(2) and is the leader of one of the current ongoing RCTs comparing two mechanical ventilator modes in the NICU. She has 80% protected laboratory time on a 5-year Mentored Career Development Award from NHLBI.

Gloria Pryhuber, MD Associate Professor of Pediatrics in Neonatology. Dr. Pryhuber received her MD and Pediatric training with Frank Oski from Syracuse and joined our faculty in 1994 after completing her fellowship and Proctor Fellow research training at the University of Cincinnati with Dr. Jeffery Whitsett. While her major research effort is in the laboratory (as well as her publications-- see biosketch), she is a valuable member of the Clinical Trials Group where her insight and critical thinking are a constant stimulus. The synergy between lab and nursery embodied in her work, is characteristic of our Division. She is protected for 70% of her time in research, and we believe her current R01 application will be funded in Sept.

Timothy Stevens, MD Assistant Professor of Pediatrics – Dr. Stevens completed his MD and Pediatric training at the University of Rochester. After an interlude at Laughlin Air Force Base in Texas, he returned to Rochester for his Neonatology training. We feel fortunate to have recruited him back to Rochester this year from Syracuse where he went to work following training. He is just starting to develop his publication record which is on his Biosketch.

Gary Myers, MD Professor of Pediatrics and Neurology - Dr. Myers directs the High Risk Follow-

up Program for our region. He received his MD from the University of Kansas, and his Pediatric training and Neurology training at the Children's Hospital in Boston. He became board certified in Neonatology in 1978, and after practicing as a Neonatologist for several years, has directed his efforts to the Neurologic sequella of prematurity, asphyxia, neonatal stroke and prenatal and natal toxic exposures. He is probably best know internationally for the work being done on mercury exposure in the Scheyelles Islands, however in Rochester he is beloved by parents and pediatricians who rely upon his skills as a Neurologist in follow up clinic. Dr. Myers is dedicated to the Neonatal Continuing Care Clinic and Follow up Program which is described in detail in section 5. He assumed its directorship in1993 and has assisted the Division in sorting out the tremendous backlog of data that had been collected on paper. The publications will now be forthcoming,(6) and an annual report is now being produced on even years. (Letter of support and commitment is attached.)

3. Available Population:

A. Regional Deliveries

The referral area for the neonatology program at the University of Rochester is the eleven-county **Finger Lakes Region of New York State**. Within this region, there are four hospitals in the immediate Rochester area and 14 hospitals in the outlying region, all of which have well developed relationships with our Perinatal Program. A non-regional Level II+ Intensive Care Nursery in Elmira staffed by an independent group of Neonatologists serves the 5 southernmost counties, approximately 1.5 hours south of Rochester. We enjoy a good working relationship with that group that accepts transfers from the hospitals in their immediate area, and we continue to serve as their regional referral center for unusual cases requiring advanced sub-specialty consultation. There are approximately 16,000 infants born each year in the 11 county catchment area and about 1,800 of these are within the Level II+ hospital's region.

Strong Memorial Hospital(SMH) is the designated Perinatal Regional Level III/IV Neonatal and High Risk Obstetric Referral Center. Thus, most predictable high risk deliveries are maternal referrals and are delivered at SMH. Unexpectedly sick term infants born in the region are brought in by our transport team. Mothers with threatened preterm delivery are cared for by our perinatologists, and if successfully brought past 34 weeks gestation, are referred back to their primary physicians for further care, thus ensuring good will and continued cooperation with Region. Deliveries at SMH are therefore disproportionately high risk and a mixture of private and medicaid patients.

The characteristics of the inborn population from 1999 are shown in Table 5 below. Over the past 5 years, the annual number of deliveries at Strong Memorial has been relatively stable at a mean of 3657: 1995–**3800,** 1996–**3603**, 1997–**3518**, 1998–**3729**, 1999–**3621**

Table 5: Characteristics of the 3621 Births at Strong Memorial Hospital in 1999

(3513 live births and 108 still births)

0.6%	received no prenatal care
72.7%	received prenatal care starting in the first trimester
32.1%	had Medicaid or no insurance
2.6%	had mother's age <17 years at the time of delivery
20.6%	of labors were induced
21.7%	of deliveries were Cesarean
2.9%	of all live born infants were products of multiple births
17.5%	of births were admitted to the NICU
67.2%	of mothers stated that they planned to breast feed
1.0%	of mothers had insulin requiring diabetes

7.4% delivered after rupture of membranes exceeding 24 hours
13.5% of all infants had a birth weight of <2500g
20.7% of infants whose mother was Black were <2500g birthweight
4.2% of all infants had a birth weight of <1500g
6.3% of infants whose mother was Black were <1500g birthweight
15.8% of infants were <37 weeks gestation
1.4% of infants had a 5-minute APGAR of less than 6
20.0% mothers smoked in pregnancy

The ethnic distribution was 73% Caucasian, 24% Black., and 3% Hispanic/Asian/other.
Insurance status was 31% private or HMO, and 59% Medicaid or Medicaid Managed care.

B. NICU Admissions

It is the goal to transport all high risk infants to Strong Memorial before delivery, but of course not all pathology is predictable. A regional transport service is provided by SMH, and trained Nurse Transporters together with a respiratory therapist travel to stabilize and return these infants using cell phone contact with the Medical Control physician. A Neonatology Fellow accompanies the team if the infant is particularly unstable (~15%).

Table 6: NICU admissions over the past 5 years

Year	Total Admissions	<37 wk	Transports	Transports<34 wk	<1500g
1995	1093	513	244 (22%)	35	155
1996	1024	473	208 (20%)	42	163
1997	1202	497	217 (18%)	35	140
1998	1296	525	236 (18%)	40	185
1999	1196	512	254 (21%)	31	170

As a quality assurance marker, we follow the number of <34 weeks gestation infants who are transported. We feel the program is particularly successful since there are only an average of 36 infants/year, and we know that about half of them come from our Level II center at RGH that is permitted, by agreement (for now), to deliver infants of 33 to 34 weeks.

Table 7 gives the gender and ethnic distributions for recent enrollees in research projects, as well as the <1500g infants who could have been in the GDB (Section 12 on Women and Minorities).

Table 7: Demographics of NICU Admits Enrolled in Recent Trials and Relevant Comparisons

	Caucasian	Afri-Am	Hispanic	Native Am	Asian	Total
National Average[a]	83.1%	15.4%	<1%	<1%	<1%	
Monroe County[a]	84%	12%	4%	0.2%	2%	
SMH-Rochester[b]	75%	19%	4.9%	0.4%	1%	
VLBW (National)[c]		37%				
Res. Enrollees	64%	30%	2.3%	0	2%	
"816 GDB infants" 1995-1999: 5 yrs	60.4%	34.1%	3.8%	<0.1	1.2%	53.8% male

[a] Democrat and Chronicle, Gannett Newspaper May 21, 1995
[b] Office of Clinical Practice Evaluation, Strong Memorial Hospital
[c] National Center for Health Statistics. *Monthly Vital Statistics Rep.* June 29, 1989;38:(No 3, suppl) 42-43

The insurance distribution of NICU admissions which include both inborn and transports, differs from the distribution of insurance from all deliveries (Table 5) because Medicaid patients more often deliver infants requiring NICU admission. For all NICU admissions (1999), there were 35% Medicaid or Medicaid managed care, 53% Health Maintenance Organizations, 8% Private Health Insurance, 4% other.

4. Maternal-Fetal Medicine Division

A. Inpatient Services

SMH with an annual delivery rate of 3600-3800 is the Regional Perinatal Center for the 11-county Finger Lakes region of upper New York State. The Maternal-Fetal Medicine (MFM) Division has been under the directorship of James Woods, M.D., Professor of Obstetrics and Gynecology since 1986 and consists currently of seven clinical faculty members. This division is the only group of perinatologists in the region practicing exclusively high risk obstetrics. The MFM Division draws its high risk obstetric population from a combined regional delivery population from 18 hospitals of 16,000 births per year. Written contracts with these hospitals for patient referral have existed since1975. As of January 1999, this division is the single Perinatal Group for all three HMOs in the region and has daytime perinatal centers in two of the largest hospitals (SMH, Rochester General Hospital). At night, a perinatologist stays in the hospital at SMH, overseeing high risk care for the region. Because of this unique design, any high risk patient transferred to Strong Memorial comes immediately under the care of the Perinatal team. The obstetric facilities on the 3rd floor of SMH, adjacent to the NICU have recently been renovated completely (1996-98) and consist of:

1) A seven bed high risk labor-delivery-recovery (LDR) unit and a four room triage area.
2) Twenty-four hour ultrasound and obstetric anesthesia services
3) Two 14-bed labor-delivery-recovery-postpartum (LDRP) units for less acute obstetric patients over 37 weeks' gestation.
4) A 26-bed antepartum high risk or postpartum cesarean section unit. Each room is private, thereby allowing overnight stays for family members.

B. Outpatient Perinatal Services

1) A newly built (1996) ambulatory center attached to the hospital. The fifth floor is devoted exclusively to OB/GYN, with a six-room ultrasound unit, and a three room fetal monitor unit in the perinatal center. All ultrasounds are acquired electronically, and transferred for permanent storage. All fetal monitor tracings also are computer acquired and stored.
2) A second center, South Clinton, approximately ¾ mile from SMH has a three-room ultrasound linked by T-line to SMH. All ultrasounds can be transferred back and forth between SMH and the South Clinton site for immediate consultation between perinatologists.
3) The Perinatal Center provides state of the art *in utero* diagnostic and therapeutic services and coordinates these efforts with a strong Division of Genetic Counseling, a multidisciplinary **Fetal Therapy Committee** and an especially sensitive Perinatal Loss Program. The Fetal Therapy Committee meets regularly to present and discuss undelivered cases of anomalies that have been detected *in utero*. Pediatric surgeons, obstetricians, neonatologists, chronic care pediatricians, neurologists, pediatric cardiologists, pathologists and geneticists attend these stimulating conferences and the results and recommendations are written up and communicated to referring obstetricians.

C. The MFM Procedures over the past years from several viewpoints are shown in the following table.

Table 8: Perinatal Procedures Over Time

Year	Prenatal Ultrasounds	Preeclampia	C/S	diabetes	3rd Trimester Bleeding	Deliveries < 34wks	all deliveries by MFM faculty
1995-96	9,015	252	725	154	114	291	477
1996-97	9,168	258	743	145	140	292	502
1997-98	9,460	313	759	141	132	298	614
1998-99	12,772	348	805	173	131	288	714

D. Maternal-Fetal Medicine Network Collaborator:

James R. Woods, MD will be the Maternal-Fetal Medicine Collaborator with the proposed Neonatal Network Center. He is the Chief of the Division of Maternal-Fetal Medicine and Associate Chair of the Department. He is ultimately responsible for the Perinatal Database, and works closely with Dr. Christopher Glantz, Associate Professor of Obstetrics and Gynecology, one of the Perinatologists who is the Director of the Perinatal Database System and coordinates this with the New York State database system. Dr. Woods did his Perinatal Fellowship with Drs. Brinkman and Assali at UCLA. After 5 years in San Franciso at Letterman Army Medical Center, he joined the Faculty in Cincinnati where he established a national reputation for his work on pregnancy loss and grieving, publishing the first edition of his book in 1987.(37) He was recruited to the University of Rochester to head the Division of Maternal-Fetal Medicine in 1986, and became a full Professor and Associate Chair in 1990. We feel fortunate that he has remained dedicated to this role, having turned down a Chairmanship to remain in Rochester, improving Perinatal Care in our region. Dr. Woods has had R01 funding to the study of the effects of cocaine on the mother and fetus, and many publications. However his true mission is the provision of education for the improvement of care for pregnant women throughout our area and the nation.

E. Additional Maternal-Fetal Medicine Faculty

In addition to the Division Chief, there are six other Clinical Perinatal Faculty, each of whom brings special skills and knowledge to the team.

J. Christopher Glantz, MD is Director of the Perinatal Database and coordinates the regional outreach and education programs in our immediate Region of 18 hospitals.

Devereux Neil Saller, Jr. MD is both a Perinatologist and a Geneticist and heads the Prenatal Counseling program. He is also director of the Maternal-Fetal Fellowship, and an insightful and helpful colleague on any problem case. He has merged the Maternal-Fetal Medicine and Reproductive Genetics programs in our region.

Thomas McNanley, MD is the Director of the Outpatient Obstetrics and has helped to reorganize the outpatient high risk patient care area improving efficiency.

Cesar Barada, MD is a collaborating perinatologist based at Rochester General Hospital

A. Gordon Fry, MD completed his fellowship at the Vermont Medical Center and has a special interest in the trophic hormones responsible for implantation.

Eva Pressman, MD from Johns Hopkins University has a research interest in diabetic pregnancy.

Additionally: Richard Miller, Ph.D. is an active member of the Division, and runs the Perinatal Environmental Drug Exposure Consultation Service (PEDECS), a program established in 1987 as one of two in New York State. Dr. Miller provides teratology information services to obstetric patients from all parts of New York State concerned about drug exposure risks during pregnancy.

Research within the Division of Maternal-Fetal Medicine focuses on clinical laboratory studies involving qualitative HCG and gonadotropin assays, plasma progesterone, L/S ratios, phosphatidyl choline and glycerol, sperm glutinization and mobilization, luteinizing hormone quantitation and plasma estrogens. A human placental perfusion model and trophoblastic cell culture system is available through the laboratory of Richard Miller, Ph.D. within the Department of Obstetrics and Gynecology and Division of Maternal-Fetal medicine. Dr. Woods has initiated pilot studies developing preliminary data for the currently under review project on antioxidant supplementation in pregnancy to improve the strength of the fetal membranes.

F. Collaboration among services:

Clinical

SMH enjoys a long-standing personal and professional relationship between perinatology, neonatology, and OB anesthesia, pediatric cardiology, pediatric urology, and pediatric surgery. Weekly joint teaching conferences and weekly prenatal diagnosis committee meetings permit unobstructed communication which, over the past 15 years, has served upper NY State patients well. Philosophically, no town-gown conflict exists. The MFM Division has been a referral-only group since 1987. The MFM Division offers no competition to general OB-GYN groups in the region for low and moderate risk patients. Moreover, if patients transferred to the MFM group reach 34 weeks' gestation, and have passed the purpose of the obstetric transfer (preterm labor, for example), they are transferred back to their general OB-GYN undelivered. The PAL phone line (Perinatal Advice Line) was established in 1995. Any physician (internal medicine, OB/GYN, family practice) who calls between 4 p.m. and 5 p.m. Monday through Friday, immediately will be connected to a perinatologist assigned to the PAL line that day to answer questions regarding patient care.

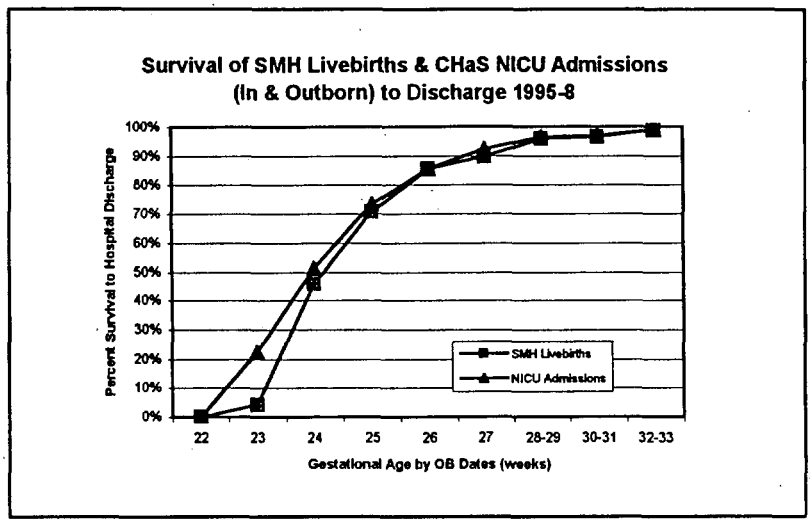
Research:

While the Neonatal and Perinatal faculty collaborate regularly in patient care, collaborative efforts have been less extensive in research. Two valuable Observational Studies have been jointly published., in particular the one documenting the incidence of cocaine positivity among a comprehensive, anonymous consecutive sample of "normal" newborns and NICU admissions has been widely referenced.(38,39) The randomized controlled trial of amnioinfusion for thick meconium fluid was successfully conducted with neonatal collaboration and demonstrated a clear neonatal benefit from amnioinfusion.(40) In addition, faculty have collaborated on several interesting case reports that are instructive,(41-46,50,51) that have built communication beyond immediate patient care. Most recently, Dr.Woods has developed a deep interest in the oxidant resistance of the fetal membranes and PROM. He has developed a collaborative grant, including R Guillet, MD, PhD from the Division of Neonatology. The proposal is under review with NICHD.

5. Facilities and Clinical Capabilities

A. SMH NICU

The NICU at SMH is the major referral facility for sick infants in the Finger Lakes Region of Upstate New York. Figure 1 at the right shows survival for the lowest gestations for NICU admissions



from 1995-1999. Over 1000 infants have been admitted to the NICU each year for the past five years. SMH opened a newly expanded and renovated state-of-the-art NICU in December 1994. In addition to the patient care areas, there are 4 isolation rooms, family and consultation rooms, x-ray developing and viewing areas, a blood gas room, charting areas and a small resource room.

The nursing requirements and ratios conform to the standards of the GUIDELINES FOR PERINATAL CARE from the American Academy of Pediatrics and the American College of Obstetricians, and acutely ill infants are normally admitted with 1:1 or even 2:1 nursing until stabilized. The usual nursing to patient ratio is 1:3 to 1:2.

Midlevel Provider Care from Housestaff and Nurse Practitioners is supervised by Neonatology Fellows and Faculty. A set of care Guidelines is reviewed and reprinted each year as a guide for the Housestaff in initiating care. These were developed by the Neonatology Faculty and Staff to bring a relatively uniform approach to the care of infants as attending physicians rotated. This helps keep approaches during clinical trials relatively similar.

Integral to the NICU function is the retrotransfer program whereby we return infants to the hospital of intended birth, when they no longer need intensive care. This allows families to be closer to their recovering newborns. The support and teaching we provide in relation to this program includes the National Resuscitation Program and has enhanced quality of care throughout our region. Because of the good will engendered, continuation of data collection for infants being followed in protocols has not been a problem.

Full support from respiratory therapy is provided around the clock, and they are responsible for all ventilators, transcutaneous monitors and blood gas determinations. Ventilation is provided mostly with Siemnan's Servo and VIP Bird ventilators, with a heavy emphasis on the use of CPAP and nasal cannula flow. Advanced technological services routinely available include Jet and Oscillatory Ventilation, inhaled nitric oxide and extracorporeal membrane oxygenation. Nursing care for infants of ELBW is provided in high humidity incubators ("Dewettes") within a target of 2 hours following birth, but more acutely ill larger infants are nursed initially in open warmers. Respiratory Therapy has been extremely supportive of our research over the past 17 years and are actively involved today and committed to continuing that support. (Letter provided)

B. Support Services

Imaging Services: Ultrasound is available daily throughout the week, and on weekends by request. Routine requests are performed on the night of request Sun. through Friday. Images are captured digitally and viewed in an x-ray reading room in the NICU. X-rays are always available, and these also are stored digitally and can be manipulated on screen in the NICU reading room, but in addition, printed films are also provided and kept in the NICU on an alternator with prior films throughout hospitalization. Pediatric Radiologists round with the Team daily, 7 days a week, reading all films from the preceding day.

Available within hours on any day are CT scanning (spiral), and within a day or two, MRI imaging. Continuous EEG monitoring is available through the Department of Neurology and the Comprehensive Epilepsy Center. If necessary, 24 hour EEG recording with simultaneous videotape recording is available.

Pediatric Sub-speciality support is readily available from Pediatric subspecialists in Cardiology, Cardiothoracic surgery, Infectious Diseases, Endocrinology, Gastroenterology, Hematology, Nephrology, Surgery, Neurosurgery, Orthopedics, Pulmonology, Genetics and Metabolism, Immunology, Early Intervention, Critical Care, Social Services and Ethics.

The Pharmacy provides unit dosing for all infants around the clock and prepares intravenous alimentation solutions daily. In addition the Investigational Drug Pharmacy tracks and dispenses investigational drugs and placebos and is capable of performing randomizations 7 days a week. They are

accustomed to working with drugs under IND and FDA audit procedures. They are supportive of our research endeavors, are also able to research and perform manufacturing locally of special drug preparations, and have provided a letter of support, with an accompanying description of their services.

Nutrition Support is provided through the Pediatric GI service and 1.0 FTE certified nutritionist (two individuals) who round daily with the NICU team Mon.-Friday. They assist in preparation and ordering of intravenous nutrition, and optimizing enteral feeds. They provide formal consultations with particularly problematic infants, and are backed up by the Pediatric Gastroenterology service. They have assisted in performing research protocols, and have offered excellent critique of protocols under development.

C. Neonatal Follow-up Program

The Neonatal Follow up Program at the University of Rochester Medical Center/Strong Memorial Hospital has been established since 1978 and is collaboratively sponsored by the Division of Neonatology and the Strong Center for Developmental Disabilities. The program has three major goals:

1. To provide early detection of abnormal developmental and neurological outcomes so that referral for services can be accomplished.
2. To provide data on the long-term outcome of babies discharged from the Neonatal Intensive Care Unit, which includes completion of evaluations of infants in research projects.
3. To provide training to health care professionals and students in NICU follow-up.

The Clinic is a multidisciplinary evaluation service for infants at highest risk for or previously identified as having a developmental disability. It does not provide primary care for infants but works closely with the primary care provider to ensure comprehensive care for the children and their families. A specified list of high risk infants believed to be at increased risk of neurological and developmental problems are brought into clinic and examined by a team at 3-9 months corrected age. These infants are <32 weeks gestation at birth and those with a neurologic disorder or severe illness in the neonatal period that predicts a high risk outcome (Example: ECMO). These infants represent about 20-25% of NICU discharges. All infants who have been enrolled in our randomized controlled trials requiring follow up are seen in this clinic. The Neonatal Continuing Care Clinic (NCCC) has a multidisciplinary team consisting of a neonatologist, neonatal fellow, nurse practitioner, neurologist, psychologist, family liaison advocate, and social worker who evaluate each infant. The Infanib and Bayley Scales of Infant Development II are most often used. A Nutrition Consultant is available on call.

The Tracking Program follows all babies discharged from the NICU, including those seen in the Clinic. The program consists of questionnaires sent to parents and primary care physicians at regular intervals during the child's first five years of age. The data collected from these questionnaires are used to support various research efforts by a number of disciplines as well as support parents and primary care physicians with follow-up. The tracking program currently follows approximately 5000 babies. Approximately 1100 of that 5000 are followed in the Clinic.

Compliance with Clinic Appointments Plans for return visits are made prior to discharge and the NCCC staff attempt to compile a number of alternative phone numbers and names of relatives to assist in tracking down young mobile familes. When an appointment can be confirmed by phone call, missed appointments fall to extremely low levels, and therefore great effort is put into these calls. The average number of infants meeting clinic criteria varies from 210 to 270 per year, and the number actually evaluated varies from 175 to 230. Aggressiveness of rescheduling depends on the circumstances. Infants from longer distances who are doing very well and have excellent pediatricians comfortable with doing developmental screening are not pursued. Thus we never approach 100% follow up. However, aggressiveness of locating and evaluating infants who are in study protocols is quite different. A former social worker, affectionately

known as "our bulldog" has been able to track and locate our former patients at all ages almost anywhere in the world. We have often completed evaluations when families return at holidays to visit relatives in Rochester. A small source of funds for travel costs is always budgeted in each grant with follow up and sending a taxi for the family (after reminders) has also been successful. There are as many tricks to success as there are families.

Funding sources to support the NCCC and Tracking program are multiple. A New York State Education grant is renewed each year and provides partial funding of a secretary/data entry clerk and family advocate as part of the resources for referral to Early Intervention and early detection of infants who need that referral. Health insurance is billed for the evaluations performed in clinic, but we have a commitment to our families that they will not incur any out of pocket costs. Presently we have just received approval to bill as a State Approved early intervention evaluation center which will help to defray some costs as well. However, it is quite clear that the NICU income from physician billing supports the majority of the Follow up program, and will continue to do so.

Policies for research in this clinic: It is clear from the material provided above that the Follow up program has the highest commitment to completion of Follow up data for research protocols.

D. General Clinical Research Center (CRC)

The CRC at the University of Rochester is a long established and successful CRC that has contributed a great deal of knowledge to the literature, particularly through metabolic studies and several unique toxicology protocols. They can not care for an NCIU infant in the CRC per se, but they have, since the funding of our 10 year SCOR grant, provided partial support to a research nurse on a "Scatterbed" basis. Support for 0.2-0.6 FTE has been provided for a nurse whose responsibility is to monitor and participate in the nursing responsibilities of the GCRC approved protocols conducted in the NICU. A separate Pediatric GCRC is not a part of the CRC in Rochster. The off-site scatterbed nurse may do assessments and procedures, but none of the study coordination or data entry roles/time can be supported by the GCRC..

If our proposal is accepted by the Network, it is clear that the protocols that our research nurse is now doing will come to an end relatively soon in the funding cycle. Depending on the number of protocols and the work involved, it is expected that more than one research nurse will be needed to complete all the work. However, a very large proportion of the work to be done falls outside of nursing per se and is not allowable by the CRC funding mechanism. To the extent that CRC funding can support a research nurse off site, we would continue to seek those funds. However, this will have to be carefully negotiated depending on the degree of nursing time needed for the commutative set of protocols being conducted. (See also Section 7 below on Research Nurse).

The CRC has also been very helpful to our Clinical Trials Group in providing statistical consultation in the planning process and sample size determination phases of a trial. Their critique and comments in reviewing protocols has also been very helpful. We are pleased that the CRC has recently learned that it expectes to receive funding on the next 5-year cycle following their site visit in April 2000. We hope that we will have a continuing productive relationship with the CRC for many years to come.

E. Special strengths:

The extensive ties with basic bench through the Division Faculty have been pointed out and are a special strength of this application. BPD is a disorder we all seek to eliminate, and the science programs that our faculty conduct in understanding pulmonary inflammation, mechanical strain and oxygen toxicity are self evident. Beyond BPD, it may prove of interest to the Network to pursue a question of toxicology at some point. For example, thimerosal in vaccines is certainly under scrutiny and the Rochester Toxicology Department probably knows more about mercury toxicity than any other University. Other substances are likely to be questioned as well, and our links with toxicology would make us an ideal consultant.

An additional special resource worth noting is the new Aab Institute for Medical Research at the University of Rochester Medical Center. Newly opened (1999), this state of the art facility for basic science and translational research includes Core facilities for transgenic and knock-out mice, confocal microscopy, peptide sequencing core, oligoprobe preparation core, electron microscopy, and the many laboratories of the individual, internationally known investigators. Should protocols arise that require the collaboration of such scientists, Rochester has a long standing institutional tradition of co-operative ventures and shared research. These investigators and facilities would be an available resource.

GroupAge	<20 yrs	20+ yrs
White, non Hispanic	72	1596
Black, non Hispanic	128	408
Hispanic	41	120
Asian/Pacif Island	1	70
Native American	0	3
others	5*	18#

(others* = 3 Laos, 1 Soamli, 1 Thailand
others# = 1 Egypt, 1 Sudan, etc.)

6. Data Systems for the Obstetric, MFM and Neonatal Services

Databases in 2000 have become increasingly interlinked and easier to use. We currently have several interactive databases and resources for queries, some of them parallel, and using two databases to answer the same question enables us to assure ourselves of more accurate answers and detecting unexpected interesting glitches in database definitions. (See example in Section 1, Table 4 where the definition of "inborn" varied between the obstetric and neonatal databases in regards to infants born in the emergency room.) The databases available to the PI are described below.

A. Perinatal Data System (PDS) and New York State Regional Perinatal Database

This PDS is funded by a foundation and run by the obstetrics department and actually produces the data from SMH for the NY State Regional Database. Information collected is described in Table 9 and includes basic data from the Birth Certificate and normal newborns.

Table 9: Data collected by the Perinatal Database and/or NY State Regional Database

Mother's full name, payor, physician in attendance, certifier for birth certificate; date of first prenatal visit, and number of visits; mother's ethnicity, prenatal lab results including blood type, antibody screen, hepatitis B testing, syphilis testing, HIV testing, drug screening if done, time of labor onset, time of second stage, time of delivery and time of third stage complete. Mode of delivery. Last menstrual period, estimated gestational age based on dates, gestational age based on ultrasound and when that ultrasound was done. Whether AFP screening was offered and if done. Maternal complications of pregnancy, labor and delivery. Maternal analgesia/anesthesia. Satisfaction with prenatal care, breast feeding plans. Scalp pH if done. Maternal smoking status, multiple births. Father's full name, marriage status, age, level of education, whether pregnancy was planned, infant's full name, date of birth, place of birth, hospital of birth, Apgar scores, resuscitation used (none, blow by oxygen, positive pressure bag and mask, intubation, drugs used (if any), chest compressions), location in hospital where infant was admitted (NICU, birth center, nursery) infant's medical findings within the first 24 hours following birth (resuscitation, admission to NICU, major anomalies). Birth weight, head circumference and length at birth. If voided or stooled in DR. Cord blood gases.

Two coders, Donna Hayes and Elaine Spiegel have been the same coders for over a decade and collect these data. They use a data dictionary of definitions applied uniformly. Data are entered routinely and not only result in the printed Birth Certificate, and Certificates of Fetal Death, but also generate the output

for the uniform database that is reported to the state of NY electronically. These data are the basis of the Regional Perinatal Center's data for quality assurance and outreach educational programs. The Regional Perinatal Center is charged with monitoring the performance of their regional level I and II hospitals. The University of Rochester Department of Obstetrics has been involved in the state-wide planning and development of this program which is now used in all hospitals that deliver infants in New York. Data collection is electronic, using software developed for this purpose and facilitates accurate reporting. Regular outreach teaching of the coders at each hospital, and return of feedback reports comparing individual hospitals to regional averages has resulted in ever improving consistency and complete data reporting.

Example of use of the PDS: An example of the use of this database for projecting a sample size and ethnic distributions for an NIH proposal on teen pregnancies is provided here. The 1st question was, "For the most recent 8 month period, what was the ethnic breakdown of teenage mothers delivering at SMH?" The second question was "For the past three years, among the delivering women who are black and primigravida, between the ages of 13 and 25, how many had infants of BW >2500g and gestational age >35 weeks, and who were 'poor' as defined by insurance = medicaid?" The answers were:

1997: 69 1998: 64 1999: 73.

Another example is given in Section 1 where the GDB eligible infants are reported for the past 5 years. The generic annual report of deliveries produced for the Division of Neonatology each year has not included the number of live births of 400-499 grams in several past years. Therefore, I requested that the Perinatal Database provide this for me. In one day's turnaround they provided the numbers needed to complete Table 4 in Section 1D.

The PDS staff are helpful and available to the MFM Division Chief who has assured the Network of availability of the PDS staff to respond to queries and data requests. The Department Chair and Division Chief support this. (see letters)

B. The Neonatal Medical Data System (MDS) for the NICU

The MDS database serves a population different than the PDS because of the admission of outside transfers that would not appear in the PDS, and because some infants expire in the Delivery Room and are never admitted to the NICU. The Division of Neonatology uses MDS-NISII (**Medical Data Systems Neonatal Information System**, Wayne, PA) for the preparation of admission notes, daily attending notes, discharge summaries and performing regular log and quality checks of typical statistics. The system is quite flexible and able to respond to tailored queries. Many of the Neonatology Faculty and Fellows are able to query the system, and for advanced queries, we rely on Denise Houston, the systems manger and Robert Swantz, MD, the Associate Medical director and head of Quality Assurance for the NICU. Because of the large number of data elements recorded each day on every infant, there is variable stringency in the definitions used for some entries, particularly surrounding contentious diagnoses such as BPD. The data elements recorded in MDS are listed in Table 10. These data are collected by 2.5 data entry clerks from the bedside chart, seven days a week, and entered each day. As the attending physician records the physical findings, assessment and plans on the printed note with this daily data, (s)he reviews the information and gives updates and corrections to the MDS data team. These are entered on the following day.

Table 10: Data collected by the Neonatal MDS Database

One Time Entry:	
Admission Note:	Narrative, not coded
From Admission:	Coded: gestation based on physical examination, birth weight, Initial admitting diagnoses (ICD-9 plus comments)
Perinatal Data:	Coded: gestation by OB dates, prenatal care, source of prenatal care, insurance, drug exposure, mother's age, gravida, para, ethnicity of mother,

	diagnoses of mother, mode of delivery, prenatal steriods,
Discharge note:	Generated from Daily data, plus a typed narrative by systems. If hearing screen was passed (also available on separate database from Audiology).
Daily on Infant:	Weight, heart rate and respiratory rate at 0700, number of apneic events in the past 24 hours, oxygen concentration at 0700 if on oxygen, mode of delivery of oxygen/nasal cannula/NCPAP/hood/ventilator and settings on ventilator, CPAP or cannula flow. Current drugs being given (including surfactant and drugs added to hyperalimentation fluids), current procedures in place, currently active diagnoses, total intake from the preceding 24 hours (00:00-23:59) including breakdown of IV fluids, hyperalimentation, intralipids, and oral feedings by formula/breast milk and concentrations

Queries are conducted at the request of a faculty member or fellow, or if someone from outside our division has a question, they go through the Medical Director with their request. One recent example was the query to obtain data for this application: ethnic distributions of infants <1500g birth weight are provided in Section 2B above. In another example, data were required to determine the number of infants eligible for the GDB that were not inborn deliveries, and therefore did not appear in the PDS. These are shown in Section 1.

An example where the database was recently used for a research project involved a survey on the use of cimetidine in infants who developed NEC and in a matched control cohort. The MDS database was used to identify all infants with a diagnosis of possible or confirmed NEC, and also was used to screen for the use of cimetidine in those infants. A matched control group was then selected by choosing the next infant born in the same month with a birth gestation within 1 week, and birth weight within 200 grams. The selected case records and identification numbers were used to pull the medical records for the retrospective survey being conducted.

C. NEOS Data System for the Follow Up Program

Data collected in this Program are linked directly via the University ethernet to the MDS system, and to the Hospital Omega Database facilitating the Program's location of families and identification of resources used. The primary database is the NEOS which is a computerized database in ACCESS for all NICU graduates. It records information from other databases on demographics, maternal care, delivery, diagnoses, treatments, tests, and referring physicians. It also records the results of evaluations of the high risk infants in Clinic and all research infants seen in clinic each year (approximately 20-25% of discharges annually). These include the coded results of a Neurological examination, developmental testing (Infanib or Bayley Scales II), hearing and vision screening results or concerns from the chart, parent's concerns, growth parameters, and referral recommendations. In addition, concerns raised by parents or physicians on the tracking forms from each annual mailing are also entered, and the nurse practitioner in our clinic follows up with these families, offering to arrange a follow up evaluation if the primary care physician concurs.

The Neonatal Follow up Program is described more fully in the Facilities section above.

7. Research Nurse Staffing

Linda Reubens, RN , a % FTE Research Nurse, has worked with our Clinical Trials Group since 1986. She is a registered professional nurse, and former NICU nurse, responsible for performing bedside and administrative duties related to the ongoing clinical trials. Specific responsibilities have included: direct patient care activities (identification of study candidates, administration of study drugs, monitoring patients

during and after treatments, monitoring patients to ensure timely and appropriate treatment and collection of laboratory specimens, obtaining laboratory specimens from patients, documentation of treatments/ procedures), data collection, organization, coordination and retrieval of research data (including but not limited to prospective data collection, retrospective chart review, follow-up of patients transferred to other centers via telephone and site visits, maintaining an on site data base of primary research variables for specific projects), monitoring quality assurance of data (including but not limited to reviewing data collection forms from collaborating centers, verifying correctness of data in data bases maintained off-site); advisory/teaching responsibilities (in-service education for nurses and fellows as well as individual bedside teaching needs for staff); monitoring adherence to study protocols, study design/documentation and implementation, and interdepartmental communications (liaison with Biostatistics, pharmacy, medical records, GCRC).

Funding:

1986-1996	NIH SCOR/NHLBI	%	FTE	
(1989-1996	GCRC		FTE	A time when we had 2.0 research nurses and GCRC funded 0.5 of the 2.0, in some years the 0.5 was applied to Ms. Reubens
1997-present	GCRC	%	FTE	variable based on # of active protocols
1997-present	Divisio		FTE	variable based on other research funding sources including GCRC, and multiple intra and extramural funds for other projects.

Since 1989, support for % FTE has been provided by the GCRC for an off-site neonatal research nurse (scatterbed) whose responsibility is to monitor and participate in the nursing responsibilities of the GCRC approved protocols conducted in the NICU. A separate Pediatric GCRC is not a part of the CRC in Rochster. The off-site scatterbed nurse may do assessments and procedures, but none of the study coordination or data entry roles/time can be supported by the GCRC. Therefore, the Division has been permitted by the Chair to expend some of our resources in supporting her administrative research roles in our overall program and partial funding for this individual has also been received by small extramural and intramural grants over the years (Mead Johnson Nutritionals, Innovations in Patient care (Intramural), intramural faculty research support funds, etc.)

Marcia Dodge, RN: Research Nurse

Ms. Dodge has recently joined the Division on the ROP studies, working for Dr. Phelps on those grant funds at % FTE time. She was recruited from a pediatric RCT that will be closing in July 2000 and is skilled in data forms, data entry, obtaining informed consent and comes extremely highly recommended from one of my most trusted former Health Care Project Coordinators. As Research nurse on the ROP trials, she is being oriented by the NICU nurses at that study's expense to NICU bedside care, issues and charting. Ms. Dodge would be able to transfer increasing proportions of her % effort to the Network Trials as the ROP studies come to closure in the next 2 years, and is willing to increase her effort to % FTE as needed.

8. Proposed Network Concept: Better Evidence for Saturation Targets (BEST)

Oxygen is used daily in the NICU with the understandably popular saturation monitoring. Yet there is little evidence as to the most appropriate saturation levels for minimizing toxicity while maintaining adequate oxygenation. The consensus statement from the American Academy of Pediatrics (AAP) to target

an arterial PaO_2 of 50-80 mm Hg provides some guidance, however, it is based on minimal PaO_2 data, and not saturations.

Asking what target saturation is safe and effective has been technologically difficult because the inherent instability of sick infants makes controlling arterial oxygen at one level impossible. Recent evidence from a regional survey in north England shows that oxygen saturation targets do influence outcomes. At the right we see that a higher saturation target was associated with higher rates of pulmonary disability and ROP.(As presented at the Association for Research in Vision and Ophthalmology, May 2000, Ft. Lauderdale, FL)(47) The study has small numbers, suffers from lack of randomization and much of the data are retrospective; however they are provocative. A separate data set provides additional evidence of pulmonary harm from higher oximetry targets. The 30 center STOP-ROP study (Supplemental therapeutic oxygen for prethreshold ROP) randomized infants with moderate ROP to pulse oximetry targets of 96-99% vs 89-94% starting at a mean age of 10 weeks following birth. All infants had some degree of BPD since they required oxygen to maintain saturations over 94%. Although a benefit for BPD had been expected, instead there were significantly more infants with at least one adverse pulmonary event in the higher oximetry target group (57% vs 46%, p=0.005) (see adjacent Table).(1) Of additional interest from this study, when infants were randomized to the lower pulse oximetry range which was considered to be the conventionally treated group, in the first 24 hours following randomization, the mean saturations fell by 4 percentage points, suggesting that many NICUs were using higher saturation levels in practice.(1)

2 Hospitals in England: <28 wk Gest.(47)

Target Saturation	88-98%	70-90%
Survival	53%	52%
n surviving 1yr	65	65
Avg. Days on Vent	25	17
Avg Days on O_2	77	44
ROP: threshold	27.7%	6.2%
Cerebral Palsy	17%	15%

In the absence of reliable data, we may be causing unnecessary motor or cognitive dysfunction from too little oxygen, unnecessary ROP from too much, and unnecessary BPD from using more alveolar oxygen than is needed for satisfactory saturation. It is our responsibility to determine the outcomes of a range of potentially acceptable pulse oximetry targets in order to make evidence-based recommendations for the future care of premature infants.

The objective of the proposed study is to develop better evidence on the best pulse oximetry range for infants of ≤28 weeks gestation.

The hypothesis is that BPD will be most frequent in the group randomized to the highest target range (estimate 30%), and at least 10% percentage points lower in the lowest group. The secondary hypotheses are that a) there will be no difference (<10 percentage points) in neurological abnormalities (cerebral palsy) and learning disabilities at school age (baseline 30%) between the highest and lowest saturation groups (power to detect this 90%), and that there will be at least a 9 percentage point lower rate of stage 3 or worse ROP in the lowest saturation group compared to the highest (base rate 18%, power 90%).

Infants Randomized after ROP ~10 wks (1)

Target Saturation	96-99%	89-94%
n	324	325
pulm. deterioration	11.7%	7.7%
In hospital, 3 mo. PMA	12.7%	6.8%
On O_2, 3 mo. PMS	46.8%	37.3%
Pul rehospitalizations	12.6%	14.1%
Any pulmonary event	57%	46%

Study Design: Infants of ≤28 weeks gestation will be randomized, ideally prior to delivery, to one of three target ranges of pulse oximetry saturation in order to examine differences in outcomes between the two extremes, and seek a dose response effect from the intermediate target. The target saturations would be: 91-

96%, 85-93% and 75-90%. Study assignment would continue until saturations are over 96% breathing room air for at least one week (thus all groups are monitored to the same endpoint). This study does NOT propose to use less than 21% inhaled oxygen in this trial if saturations rise over target while breathing room air. To facilitate achieving the targets, one of the new class of oximeters resistant to motion and low perfusion artifact (Massimo SET oximetry) would be used on all study patients. The STOP-ROP study demonstrated the feasibility of using such targets and instrumentation.(1,48) Randomization would be stratified by center and gestational age to facilitate balance in the randomization. Gestation, rather than birth weight, would be used as it is hoped that randomization can occur prior to delivery in a significant proportion of enrollees.

Masking of the intervention would require altering the calibration of the pulse oximeter, and has been done in at least one study (Australian trial of supplemental oxygen for BPD), but is not likely to be acceptable in the acute care setting. All primary and secondary outcomes will be determined by masked evaluators.

The Primary Outcome would be the incidence of BPD at 36 weeks post-menstrual age (PMA), based on oxygen requirement. In order to adjust for infants that may still be receivning oxygen or not accroding to their study assignment, the "need for oxygen" would be determined as "inhaled oxygen >21% as needed to maintain a pulse oximetry greater than 94% saturation over a minimum 2 hour oximetry tracing." All infants would be tested for 2 hours.

Although a single primary outcome is traditional, there are obvious additional outcomes of equal importance. The incidence of "threshold" ROP would be recorded prior to discharge by ophthalmologists masked to the study group. The interval evaluation at the 18-22 month follow-up visit for the GDB would provide neurologic, developmental, and functional testing performed by individuals masked to the infants' original study group. These tests would be repeated at school age (7-8 years). In addition, school success and degree of academic support would be determined.

Sample size is based on a Type I error of 5%, and a power of 90% to detect an absolute decrease of 10% in the incidence of BPD at 36 weeks PMA assuming a base incidence of 30%. By taking the 500 recommended infants for each arm of a two arm trial and enrolling another 500 into the middle saturation target, more than sufficient sample will be enrolled for the primary outcome, comparing the highest and lowest targets, and sufficient sample will be enrolled for several of the important secondary outcomes at similar power. This sample size is adjusted (Bonfiorri correction) for multiple comparisons/outcomes. In addition, logistic regression or analysis of variance will be used to look for dose/response effects across the three targets. Allowing for 15% mortality and 80% follow up success at school age, the suggested sample size is increased to 600 per group (= 1800 total) to permit at least 400 infants to be evaluated in each group at school age.

The MDS database from the Rochester Center was used to query the number of infants ≤28 weeks who would have been eligible for this trial. Over 4 years, 284 infants of 22-28 weeks were admitted: 151 males and 133 females. The mortality was 23 (15%) among the males and 19 (14%) among the females. For one center to complete this study (at 71/year) would require 1800/71 = 25 years, however, if the network is able to enroll 75 infants/center in 12 centers, it would take two years.

The Data and Saftey Monitoring Board would be charged with monitoring of adverse outcomes with special sensitivity to any indications of hypoxic problems in the lowest saturation group or evidence of oxygen toxicity in the highest saturation target group (BPD, ROP). Reports for their review should include rates of protocol violation and the reasons (withdrawal from assigned group), mortality, duration of ventilator support and oxygen supplementation, use of steroids, rates of any ROP and threshold ROP, and

developmental disabilities as those outcomes accumulate. A group sequential analysis would be used to adjust for interim analyses.

Possible findings and Implications:

If as the English study suggests, the lowest saturation target group does best in both BPD and ROP outcomes with no evidence of neurodevelopmental harm, a follow on study should be planned to further explore lower saturation targets. If the highest target group does best, again there should be further studies which examine the risks and benefits of raising the target saturations further. No further study would be indicated if the middle range is best for all outcomes.

However, it is more likely that one end of the range will be best for the lungs but may not be for neurological outcomes. Formal decision making analysis to balance the risks and benefits from the infant's and society's perspective across the three ranges should clarify the issues to be balanced, this time with data, rather than rationalization.(49) For instance a small increase in BPD might be a worthy tradeoff for improved long term neurologic function.

9. Intent to Participate:

Dr. Phelps and the investigators of the Division of Neonatology in the Department of Pediatrics at the University of Rochester are deeply committed to the promotion of health care for newborns in our region as well as in the Nation and Internationally. We recognize the need for sound scientific data, and have equipoise with randomized clinical trials. We have led and are leading collaborative investigations of promising innovative therapies in neonates, and if our proposal is accepted for the NICHD Network the following plan will allow us to smoothly transition to the Network trials to which we expect to fully commit our patient population, our creativity and our diligent work.

The Rochester Clinical Trials Group:

As is apparent, multiple trials have been conducted simultaneously in our NICU, and we have a group of investigators from within our Division who meet twice monthly to maintain coordination between the research efforts in the NICU. We debate new trials, monitor the progress of each ongoing trial and oversee manuscript preparation. Minutes are kept of each meeting, and our Research Nurse, Linda Reubens provides the up to the minute data on number of eligible and enrolled infants in each ongoing study. Minutes are distributed via e-mail to each of the clinical faculty, Neonatology Fellows and our Mid-Level providers who are all master's level trained nurse practitioners or physician assistants. These facilitate ongoing communication and rapid dissemination of corrections, updates, quality issues, and other trial issues. (See figure below for the current trials in relation to the Network proposal.)

Our Clinical Trials group has developed two mechanisms to deal with potential conflicts between competing trials. The first is our own review and discussion of trials among our own group, and the second is the Perinatal Research Committee that addresses a broader range of investigators from the entire University.

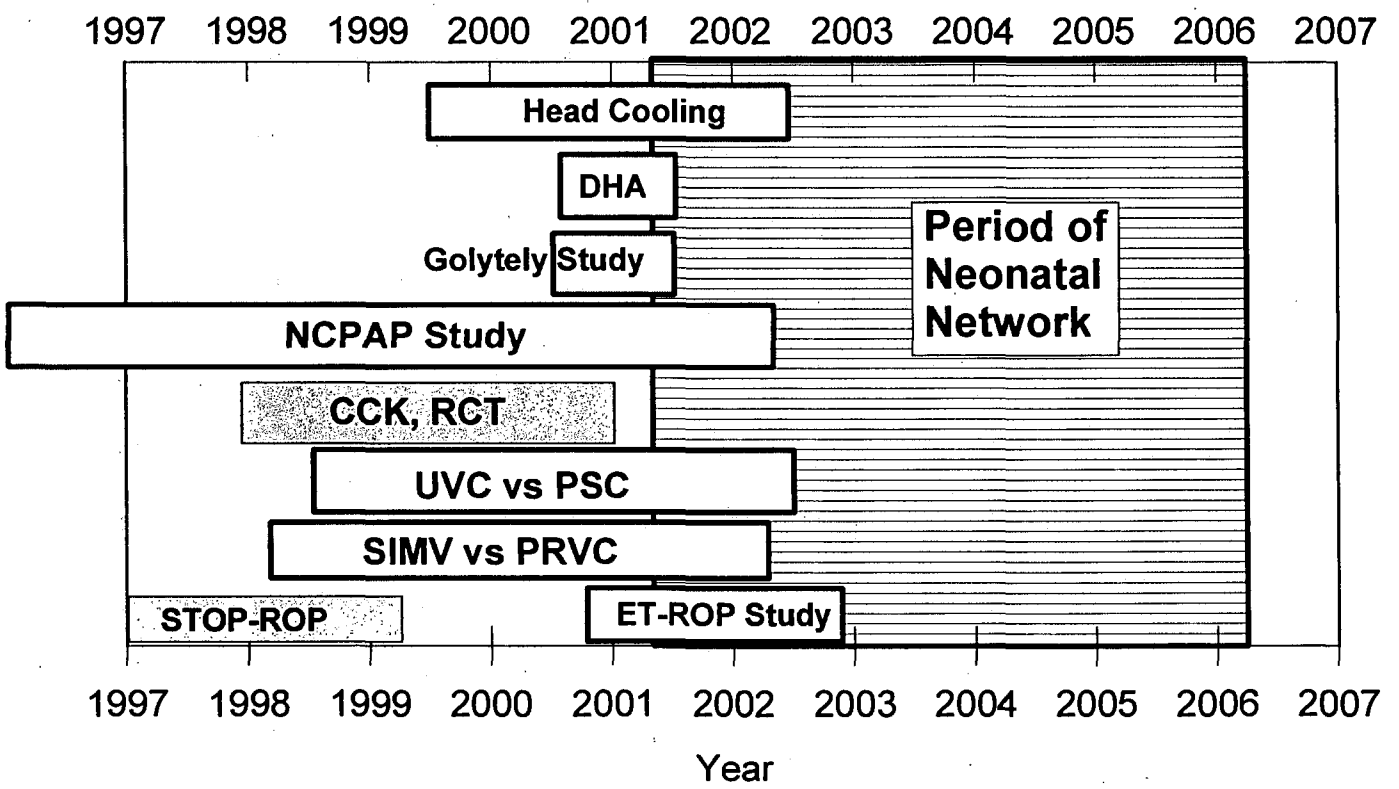
The Perinatal Research Committee is a multi-disciplinary scientific review group that reviews all proposed human research that would involve subjects or tissue samples from the NICU, the normal newborn nursery, labor and delivery, or the prepartum period. This includes psycho social research that involves questionnaires. The committee assesses the scientific merit of a proposal, its potential conflict with other ongoing studies, and potential resource use and implications for staff. The committee is composed of two representatives from Neonatology and two from Obstetrics with the chair being Richard Miller, PhD from the Department of Obstetrics. The University of Rochester Human Subjects Review office recognizes the Perinatal Research Committee and requires their project approval before final IRB approval of any perinatal protocol. Both the Perinatal Research Committee and the Division of Neonatology clinical trials groups

address potential conflicts over subjects availability with the following principals. Funded ongoing research carries the highest priority. Ongoing research has priority over planned research. Controlled trials have priority over observational studies. Faculty projects have priority over student projects, and Departments of Pediatrics and Obstetrics projects have priority over other departments. Extraordinary efforts are made to accommodate as many protocols as possible minimizing the potential ethical problems of approaching parents for more than one project, and the requests for time and effort on the part of non-research funded hospital personnel.

We have also developed a policy for simultaneous participation of a subject in more than one protocol. Infants may be enrolled in more than one research protocol with three conditions. a) The intervention for a additional study must not have any potential conceivable effect on the primary outcomes of the project the infant is already enrolled in. (For example, an observational study looking at parent stress in the NICU is unlikely to conflict with an outcome of survival in the comparison of two surfactant strategies. However, use of steroids to prevent BPD could clearly impact the outcomes in a surfactant strategy study.) b) The PI and any sponsoring agency must be informed of the potential of enrolling infants in a another trial, be provided with a summary of the protocol and approve the secondary protocol. c) Parents may not be approached to consider more than three research projects in the first week surrounding birth. This difficult decision was made based on our knowledge that many families take great pride in participating, and often new therapies that are of benefit to the patient are available only through the trial mechanism. d) Families where the population for sampling is very large compared to that needed for a trial will not be approached for more than one project.

Dr. Myers has provided a letter of support for the Follow up Program, and is dedicated to the follow up of each research subject using the Network protocols. The Division of Neonatology that financially supports the Follow up Program is also committed to its continuation.(see letters)

Timeline of Recruitment for Randomized Clinical Trials at Rochester



The time line above shows the present ongoing Neonatology trials in our center, and the projected dates for completion of enrollment. Although there are a large number of active protocols at this time, most will complete enrollment before, or very early in the Network 5-year study plans, thus "releasing" our population for new intervention studies. Project summary sheets (in the NICHD Network Webpage format) for each of these current studies are provided in the appendix to this proposal. No potential conflict with the Network's Generic Database is perceived. If we are awarded participation in the NICHD Network, we would anticipate approximately 2-3 months for each project to go through the approval process of the protocol presentation to the Clinical Trials Group, the Perinatal Research Committee and the Institutional Review Board. Many trial proposals could be submitted simultaneously to these two review committees after approval in the Clinical Trials group, and each of the University Committees meets at least monthly.

10. Departmental and Institutional Commitment

(Please see letters from Dean Lowell Goldsmith, and Chair Elizabeth McAnarney.)

The University of Rochester School of Medicine and Dentistry is an institution with a long-standing commitment to biomedical research. The University Medical Center has scientific programs of consistently high quality both in its well-known School of Medicine and Dentistry. Collaboration of faculty across programmatic and departmental lines is not only feasible but strongly encouraged. This yields an academic environment where intellectual input and scientific facilities are easily available to our NICHD research on an as-needed basis.

The Department of Pediatrics has a tradition of support for laboratory and clinical biomedical investigation and is completely supportive of our Application (see Letter). The Division of Neonatology and Department has committed to providing appropriate space for the research staff, if funded.

11. Acceptance of Budgetary Mechanism

The Division of Neonatology, the Department of Pediatrics and the University of Rochester understand and are experienced with both the U10 mechanism of grant funding and the capitation of costs according to enrollment. The University will comply with all necessary accounting practices and cooperate fully with the funding agency. (See letters)

12. Human Subjects: Inclusion of Women and Minorities

Human Subjects and The Network

Each clinical protocol that is accepted by our Center will have already been reviewed by the NIH. However, each will also be submitted to the Human Subjects Review Board at Strong Memorial Hospital (and back transfer hospitals as indicated), and must be approved prior to their implementation. The University of Rochester holds a General Assurance with the NIH, and all review procedures are in compliance with NIH guidelines for the recruitment, enrollment, and protection of human subjects, without prejudice. Risks and benefits will be closely weighed.

The University of Rochester Human Subjects Review Board was extensively reorganized several years ago along with the extensive expansion of the Medical Center's Research Programs. Separate subcommittees deal with non-medical research, medical interventions, and FDA/IND commercially sponsored trials. As a result, the Review process is efficient and effective. All faculty participating in clinical research complete a course on the ethical conduct of human research and are required to have a certification number to submit protocols. Dr. Phelps has this certification, as do most of the faulty in the Division.

The preceding application discusses our center's past and ongoing studies involving human subjects with regards to the enrollment of women and minorities, the characteristics of the available population, and inclusion/exclusion criteria for a protocol concept. This material is repeated here for clarity.

Inclusion of Women/Females:

Both male and female infants are recruited without regard to gender, but rather based on their birth weight, gestation and/or disease states. No gender differential in success of follow up is observed and ethnic balances of enrollment are shown in the Table below.

Inclusion of Minorities:

The minority distribution of premature deliveries over represents minorities as compared to Monroe County (Rochester), and over represents minorities Nationally (see Table below). This is appropriate, however, since premature deliveries occur more frequently among minorities (particularly African-Americans), than among Caucasians and Hispanics. Since our past success in minority recruitment has exceeded national proportions, special Outreach Measures are not needed for recruitment. However, we will continue to expend special emphasis on ensuring informed consent and understanding of our patient's families.

Follow up is known to be more difficult in minority groups, and therefore we utilize special outreach efforts to enable disadvantaged minorities to participate fully in follow up. These include, but are not limited to bus fare, parking vouchers, taxi transport, baby sitting assistance during examinations and small gifts/toys for the children, as well as the ready availability of a dedicated follow up coordinator who is a helpful resource and friend and advocate for the child as well as the study.

Demographics of NICU Admits Enrolled in Recent Trials and Relevant Comparisons

	Caucasian	Afri-Am	Hispanic	Native Am	Asian	Total
National Average[a]	83.1%	15.4%	<1%	<1%	<1%	
Monroe County[a]	84%	12%	4%	0.2%	2%	
SMH-Rochester[b]	75%	19%	4.9%	0.4%	1%	
VLBW (National)[c]		37%				
Res. Enrollees Male Female	64%	30%	2.3%	0	2%	 155(52%) 143(48%)
"816 GDB infants" 1995-1999: 5 yrs	60.4%	34.1%	3.8%	<0.1	1.2%	53.8% male

[a] Democrat and Chronicle, Gannett Newspaper May 21, 1995
[b] Office of Clinical Practice Evaluation, Strong Memorial Hospital
[c] National Center for Health Statistics. *Monthly Vital Statistics Rep.* June 29, 1989;38:(No 3, suppl) 42-43

13. Vertebrate Animals (Not applicable.)

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Lowell A. Goldsmith, M.D.
Dean
School of Medicine and Dentistry

June 30, 2000

Dale L. Phelps, M.D.
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave., Box 651
Rochester, New York 14642

Dear Dr. Phelps,

The University is pleased to support the Department of Pediatrics' Division of Neonatology's application to join the NICHD Multicenter Neonatal Research Network. Your Division has an outstanding legacy of multi-center cooperative clinical research beginning with the SCOR surfactant studies, your own multicenter trials in ROP, and the ongoing trails on ventilatory strategies and brain cooling for hypoxic brain injury. Your work in these areas has been a vital link in moving research from the laboratory into clinical trials, a key part of our mission. Your outstanding National Reputation in the design, conduct and oversight of randomized controlled trials should make you an extremely strong candidate for this competition.

We recognize and accept the U10 Cooperative Agreement funding mechanism for this application, and will comply with the necessary record keeping involved in the capitation supplements. We will ensure the availability of the additional space necessary to conduct the work.

The opportunities for continued collaborative research are outstanding within the Department of Pediatrics' Strong Children's Research Center and the Medical Center's new Biomedical Research Facility.

The University is proud to support this application with enthusiasm.

Sincerely,

Lowell A. Goldsmith, M.D.
Dean, School of Medicine and Medicine

LAG:bs

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Elizabeth R. McAnarney, M.D.
Professor and Chair, Department of Pediatrics
Pediatrician-in-Chief, Children's Hospital at Strong

June 27, 2000

Dale L. Phelps, M.D.
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave., Box 651
Rochester, NY 14642

Dear Dale:

I am happy to affirm the commitment of the Department of Pediatrics to the Division of Neonatology's application to join the NICHD Multi-center Neonatal Research Network. Your Division has an outstanding legacy of multi-center cooperative research, beginning with the SCOR surfactant studies and continuing through today with your current multi-center trials in ROP, ventilatory strategies and brain cooling for hypoxic brain injury. Your Division's work in these areas has been a vital link in moving research from the laboratory into clinical trials, a key part of our mission. The Department has continued to support your research nurse, in part, in recognition of her ongoing role in current research, and knowing that you will continue your efforts to achieve more extramural funding for her.

If you are successful in this competition, we will ensure the availability of additional space with appropriate telecommunications and storage to accommodate the somewhat enlarged research staff that will be necessary to perform the work. We would accept the funding mechanism of a U10 Cooperative Agreement. We will also continue our commitment to the Division's support of the Neonatal High Risk Follow Up Clinic and Tracking Program of the past 20 years, as well as the Clinical Documentation Database that has been so successful in providing a base for research, quality assurance and frequent requests for statistics. The Department's Office of Grants Administration will continue to assist you in budget preparation, compliance with Network needs surrounding capitation billing and ongoing monitoring of the grant funds.

The environment for continued collaborative research is excellent within the Department of Pediatrics' Children's Research Center and the Medical Center's new

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Biomedical Research Facility. I would hope that these collaborations will foster concepts for you to propose to the Network, should you4 application be successful.

You have my strongest commitment of support and level of enthusiasm for your application.

Very truly yours,

Elizabeth R. McAnarney, M.D.

ERM:cb

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DEPARTMENT OF PEDIATRICS—CHILDREN'S HOSPITAL AT STRONG
DIVISION OF NEONATOLOGY

July 6, 2000

Dale L. Phelps, M.D.
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Avenue, box 651
Rochester, New York 14642

Dear Dale,

The Division of Neonatology is a coherent group of faculty colleagues in the NICU (10 of us), in the lab (3 more) and in our collaborative clinical research group (2 more). We have been discussing the Neonatal Network application for about 10 weeks now; this letter serves to formally state that we unambiguously endorse and support that application. It would be hard to find a group of 10 neonatologists more experienced than we are with the joy and pain of randomized, multi-center controlled trials. Your ROP studies, our surfactant and steroids trials, and the smaller single center studies done by our fellows with our mentorship add up to extensive experience in complex clinical trials. It has been a major decision to confront the loss of autonomy in choosing the protocols that we will conduct, and to accept that our fellows will not be able to initiate trials that might compete with babies for the Network Trials. Despite these drawbacks, we feel commitment is worthwhile because of the tremendous advantage the Network has in testing new, or old, interventions in a timely manner. We have been particularly excited that as some of our work at the bench and in animal models moves into pilot studies, the Network will be ideally situated to bring the promising new ideas to rapid, definitive testing in the NICU.

If this application were submitted just last month, you would have been Division Chief, writing this letter yourself. I know you've stepped down after 10 years because your heart is in your research, and that you are extremely excited to be returning there. As an interim Chief, I discussed this proposal with the Department Chair, Elizabeth McAnarney, to be certain that the Department would continue to provide full support to my Divisional Decisions. I was completely reassured that, as ever, our Department stands solidly behind the Division's commitment to the Follow-up Program as they have since I started it with Don Shapiro in 1978. Also, I was reassured that we have full control over the Clinical Documentation staff, who permit us to have such ready access to the NICU statistics, and in the performance of the daily chart work.

In short, the NICU, the Follow-up Program, the database, our population and the division clinicians are integral parts of our division that, together with your experience and the support of the Maternal-Fetal Division, makes Rochester an outstanding center for the Network.

We are excited about the opportunity to work with the NICHD Neonatal Network, and we hope that your application on our behalf will be selected for inclusion in the next 5-year funding cycle. You have my strongest commitment of support and the enthusiasm of our division for your application.

Sincerely yours,

BM

William M. Maniscalco, M.D.
Professor of Pediatrics
Interim Chief, Division of Neonatology

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Children's Hospital at Strong
Division of Neonatology
Neonatal Continuing Care Program

5 July 2000

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave, Box 651
Rochester, New York 14642

Dear Dale,

The Division of Neonatology developed the Neonatal Continuing Care Program (NCCP) in the late 1970s. I have had the privilege of being the Director since I joined your Division in1993. The original design of the NCCP was remarkably good and we have only made minor modifications over the years. It has functioned in a cost efficient manner and apart from the challenge presented by the rapidly changing technology of this decade for databases has been a program that very effectively accomplishes the following:

1) Evaluates the highest risk infants in a multi-disciplinary clinic, permitting early intervention referrals and therefore a valuable service to the patients while collecting data.

2) Tracks the progress of all NICU graduates through mailed questionnaires to primary care physicians and families utilizing specific questions and open-ended comments, thus providing long-term follow-up data and detection of cases where there is concern by family or physician. Again this is an excellent patient service.

3) Provides a teaching and training environment for subspecialists including neonatal fellows, social workers, physical therapists, psychologists, neurologists, nutritionists, pediatricians and other disciplines.

4) Provides a clinic where each subject of a research protocol receives the predesignated formal evaluations for that protocol. Thanks to the relatively stable population of Upstate New York and the strong tendency of families from this area to return home, our tracking Social Worker, Joan Merzbach, has consistently found 100% of all surviving research subjects. This has enabled us to have unprecedented success rates of follow up in our studies of over 95% (not all families consent to follow up evaluations, even when found).

I have always been impressed by the commitment and support that the NCCP has had from the Division of Neonatology and the Department of Pediatrics. I recognize that the NCCP has been financed largely through the Neonatology Division's resources with additional support from the New York State Department of Education grant for the O-2 early detection program. I have been assured of the ongoing commitment of Dr. McAnarney as the Chair of Pediatrics and Dr. Maniscalco as the Division Chief of Neonatology. In addition, we have just been approved on a one-year trial basis to be a State Approved Early Intervention Evaluation Center. The NCCP is on extremely strong footing conceptually and financially and our location in the Ambulatory Care Building contiguous with the hospital is convenient for family and staff.

On behalf of the staff of the NCCP, let me express our excitement at the opportunity to work with the NICHD Neonatal Network. We sincerely hope that your application will be selected for inclusion in the next five-year funding cycle. You have my strongest commitment of support for your application and we look forward to helping you make it an outstanding success.

Sincerely Yours,

Gary Myers, MD
Medical Director, Neonatal Continuing Care Program
Professor of Pediatrics and Neurology

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DEPARTMENT OF OBSTETRICS-GYNECOLOGY

David S. Guzick, M.D., Ph.D.
Henry A. Thiede Professor
Chair, Department of Obstetrics and Gynecology

July 5, 2000

Dale L. Phelps, M.D.
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave, Box 651
Rochester, New York 14642

Dear Dale,

I was pleased to learn of your intent to apply to become a participating center in the NICHD Neonatal Research Network, and support your application fully. The Department of Obstetrics and Gynecology has a broad Clinical, Educational and Research agenda, and I know you've worked closely with James Woods over the past 16 years to ensure excellence in obstetrical care in the Fingerlakes Region. As the designated New York State Regional Perinatal Center in this area, our Department takes its responsibilities very seriously to monitor care in our 18 referring hospitals, to provide regional statistics related to pregnancy and childbirth, and to continue outreach education.

The Maternal Fetal Medicine Division is a major strength of this Department, and we have an unswerving commitment to its ongoing program. They have expanded over the past five years both in number of faculty, and the outreach efforts that are so important to our region. Not only does the smooth running maternal transport and referral system for high risk pregnancies result in outstanding patient care, but the respectful treatment of referring physicians by the perinatologists and return of their patients with outstanding communication ensures the ongoing success of the program. Because of this system, you can be confident of seeing in your NICU, almost all high risk infants delivered prematurely in the upper Fingerlakes Region.

If you are successful in the competition, I am happy to assure you that the Department would be proud to have Dr Woods serve as your collaborator, and I know many of his colleagues feel the same. The clinical interaction that your two Divisions have on a twice weekly basis through the Perinatal Conference and the Perinatal Diagnosis Committee are unique in my experience, and foster excellent communication and working relationships.

The Obstetrical Program anticipates no significant change in numbers of annual deliveries, although we do bear some risk of a very significant increase if one of the ViaHealth HMO hospitals fails. I don't believe that could result in any harm to your plans, and may even enhance the potential to recruit if there are protocols involving low risk newborns. The high risk infants will have been transferred here anyway.

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If there are protocols that will need to coordinate with the delivery services, we will support Dr. Woods' efforts to be meaningfully involved. We recognize the essential need of the New York State Database for the Network queries for basic perinatal statistics. As you know, Rochester has pioneered the development of the obstetric arm of the database, and are now preparing to "Beta Test" the neonatal arm as well. Through Drs. James Woods and Chris Glantz, you will be provided ongoing access to this database and will be able to build queries with the statisticians who work with it..

You have my commitment and enthusiastic support for your application.

Sincerely,

David S. Guzick, M.D., Ph.D.

DSG:sed

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Strong Memorial Hospital

July 10, 2000

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave, Box 651
Rochester, New York 14642

Dear Dale,

It was a pleasure to discuss with you your planned participation in the NICHD Neonatal Research Network. You and I have been colleagues since fellowship time at UCLA in the 1970s, and I'm delighted to serve as the Maternal-fetal Medicine Collaborator on your application. Both as the Division Chief, and as a colleague, I'm happy to affirm the commitment of our Division to cooperate with you and any Network Protocols that may involve our patients. We support your application fully, and recognize the important role that the Network Program is carrying out in our Nation.

As the designated New York State Regional Perinatal Center in the Fingerlakes Region, our Division has full access to the New York State obstetric Perinatal Database and we monitor pregnancy and birth outcomes through our regular outreach programs that we share with your Division. As you know, we are the sole perinatal referral group for a 10 county region of Western New York State and draw our high risk referrals from a catchment population of 16,000 deliveries per year. We are fortunate that the referral system continues to function smoothly, as I know this is not true in many other areas of the country. Having all of the seriously high risk pregnancies "under one roof" has helped us to improve care tremendously, and I know how much having these infants inborn has meant to reducing morbidity and mortality. Through myself, Chris Glantz, MD and Tim Dye, PhD, we will ensure the ready availability of the database for your needs with the Neonatal Network. My division of seven perinatologists and one Maternal-Fetal Medicine Fellow will assure access to this high risk population.

As we discussed, I am pleased to have expanded the Maternal Fetal Medicine Division over the past ten years both in number of faculty, and in the success of our outreach efforts, so important to our region. We now have a full compliment of academic perinatologists, and are expanding our research goals. I am excited about the grant that we have just resubmitted to study the beneficial effects of nutritional intervention upon the strength of the chorioamnion with the potential to reduce premature rupture of membranes. I am interested in pursuing the neonatal evaluations you suggested for the infants of the mothers in this trial, and appreciate your Division's collaboration on this.

It is difficult to predict if the number of annual deliveries will change at Strong Memorial Hospital, the Regional Perinatal Center for this region. High risk deliveries are unlikely to decrease, due to our successful referral program. To the extent that some of our regional HMOs may consolidate delivery services over the next two years, we anticipate only a potential increase in newborn deliveries.

I am happy to be your collaborator with the Network, and I know my colleagues feel the same way. You have our commitment and enthusiastic support for your Division's application.

Sincerely,

James Woods, MD

James R. Woods, Jr., M.D.
Dean's Professor Obstetrics and Gynecology
Director of Obstetrics and Maternal-Fetal Medicine
Associate Chair, Dept. of OB-GYN

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SCHOOL OF NURSING

GENERAL CLINICAL RESEARCH CENTER

John E. Gerich, M.D.
Program Director
Professor of Medicine and Physiology

July 10, 2000

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave, Box 651
Rochester, New York 14642

Dear Dr. Phelps,

The General Clinical Research Center is pleased to support your application to join the NICHD Multicenter Neonatal Research Network - the work of the Network is precisely complimentary to the mission of the GCRC, and is an outstanding opportunity for your Department to leverage the funding and support provided by our GCRC over the past 10 years. We have been pleased to commit partial funding, albeit variable, to your Research Nurses through the "scatterbed" nursing budget of our Unit. Ms. Reubens is a dedicated and conscientious research nurse who is meticulous in her record keeping and data.

Your participation on the Advisory Committee of the GCRC has given me many opportunities to observe your insight, experience and knowledge on clinical trials. Be it pilot studies, regional trials or multicenter trials, your reviews have been on target and often raise important key questions that assist the investigators and our committee. I am certain that the NICHD Neonatal Network Steering Committee will be grateful to have your expertise.

We recognize the U10 Cooperative Agreement funding mechanism for this application, and that it will be necessary to coordinate, and possibly adjust funding efforts of the Neonatology Research nurses from the GCRC if this application is funded. We have been pleased to be able to support, in part, your Division's clinical trials effort both during the SCOR period, and in the interval since the end of your SCOR grant from the NHLBI. We pledge our continued academic, and if possible financial support.

The GCRC supports this application with enthusiasm.

Sincerely yours,

John E. Gerich, MD
Program Director
Professor of Medicine

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STRONG HEALTH

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Respiratory Care
Strong Memorial Hospital

July 10,2000

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester Medical Center
601 Elmwood Ave, Box 651
Rochester, New York 14642

Dear Dr. Phelps,

The Respiratory Therapy Department of Strong Memorial Hospital was pleased to learn of your intent to apply to become a participating center in the NICHD Neonatal Research Network. We support your application fully, and have long enjoyed working with you on the clinical trials of surfactant. Currently the participation of our Department in doing the pulmonary function testing in the ventilator trial is an important part of our role with you. In addition, we have been pleased that we've been able to rotate with the team providing the masked intubation and surfactant administration in the Nasal CPAP trial.

With Greg Hutton as the Coordinator of our Newborn Intensive Care and Pediatric Intensive Care Unit within the Department, we've felt quite pleased with the continual improvements and sense of accomplishment that this specialization has provided for the Children's Hospital at Strong.

If you are successful in the competition, I am happy to assure you that our Department will continue to be very interested in and participate in research protocols that you initiate. It is also good to know that depending on the extent of that involvement, there may be supporting funds available to offset our direct expenses specific to these activities.

You have our commitment and enthusiastic support for your application.

Sincerely,

Peter Scheibe, MBA, RRT
Director, Respiratory Care

Cc: Kathy Parrinello
Greg Hutton
File,

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STRONG MEMORIAL HOSPITAL
SCHOOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING

DEPARTMENT OF PHARMACY

Tuesday, June 27, 2000

Dear Dr. Phelps,

The Research Pharmacy is pleased to continue our support of the Division of Neonatology's research in the Newborn Intensive Care Unit. We support your application to join the NICHD Multicenter Neonatal Research Network, and appreciate that those protocols involving randomization in the pharmacy, and pharmacy management of investigational drugs and placebos will require our assistance. It is good to know that there will also be appropriate (if limited) capitation funds for this effort. We have always worked closely with your Division through its investigations of surfactants and other drugs requiring FDA paperwork and tracking of stock. Our unit has an extensive experience with IND procedures, is able to provide randomization at all hours, provision of placebos, and tracking of stock as routine matters. We also have worked closely with your research nurse, Linda Reubens, for over 12 years and appreciate her skill, knowledge and persistence. She is a real asset.

Our charges include a set up fee for new studies, a close out fee and a per patient fee (depending on the number of unit doses needed for a study). Longer studies also require a maintenance fee for the paperwork involved. These costs are negotiable and we recognize the need to minimize charges for NIH sponsored research.

In addition, we have testing and manufacturing facilities available that can help you to work out formulation and testing of perhaps novel treatments that you might like to pursue. The example we discussed, of inositol as an IV supplement, is a good example. Although federal licensing laws do not allow us to formulate prepare, manufacture and ship materials for multiple centers, we could do the basic work to determine how to safely prepare this sugar for IV administration and then share that information with other centers that have similar manufacturing capability. This would result in a considerable cost savings for your network since it would only have to be worked out once. We would have to recover our costs of the initial preparation work.

The Research Pharmacy supports your application and looks forward to working with you within the NICHD Neonatal Research Network.

Sincerely yours,

Stephen A. Bean RPh CCRC

Stephen A. Bean, RPh CCRC
Investigational Drug Service
Department of Pharmacy
Strong Memorial Hospital
University of Rochester, Rochester, NY

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Investigational Drug Service (IDS)

The University of Rochester Medical Center (URMC) Investigational Drug Service (IDS) was established in 1993. Its mission is to provide the clinical research scientists and investigators with the necessary support to assure safe and efficient conduct of clinical drug trials including compliance with federal, state, Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and American Society of Health-System Pharmacists (ASHP) requirements regarding control of investigational drugs. The IDS, which is available to all clinical investigators at the URMC, is supervised by Steve Bean, a pharmacist who has undergone thorough training and certification in the management of investigational drug trials. Due to the growth of drug related clinical research at the URMC, the IDS staff is expanding in order to serve the needs of researchers in a timely fashion. Another experienced pharmacist, Dan Cole, has recently joined the IDS staff on a part time basis. The IDS technicians are Carla Ducci and Lisa Thompson, both of whom are Certified Pharmacy Technicians.

The following paragraphs provide a synopsis on each of the specific services provided by the IDS.

INVENTORY CONTROL and STORAGE
Investigational drugs are stored in both the Investigational Drug Service and the Department of Pharmacy to ensure appropriate access, security, stability, and compliance with Food and Drug Administration (FDA) guidelines. Drug order, receipt, and return forms are maintained for all medications used in clinical trials. The IDS will order and receive shipments of investigational drugs. The IDS maintains adequate inventory levels to assure ready availability of study drug.

DRUG ACCOUNTABILITY
Drug accountability records are maintained for all study drugs received, stored, and dispensed by the IDS. Study drug supplies are inventoried monthly for quality assurance purposes. The IDS maintain records after study completion according to FDA requirements, or as specified per protocol.

PACKAGING AND LABELING
The IDS utilizes a fully computerized dispensing system to generate labels and track patient profiles. The IDS repackages medication to accommodate special dispensing and blinding requirements. Outpatient prescriptions are dispensed pursuant to a written prescription, legal in New York State, and the outpatient prescription labels meet all labeling requirements set forth by the FDA and New York State Board of Pharmacy

DRUG INFORMATION
The JCAHO requires that anyone administering an investigational drug have a working knowledge of the drug, such as its purpose, side effects, precautions, and procedures for administration. Thus, for inpatient studies an Investigational Drug Data Sheet (IDDS) is prepared for pharmacy staff informational purposes. The IDDS is downloaded into the pharmacy's main computer and updated as needed. Upon request of the Principal Investigator, an IDDS can be prepared for the medical and nursing staff. The Principal Investigator is asked to proof this IDDS before its use.

DISPENSING

Inpatient: Drug is available for most studies, 24 hours per day, 7 days per week from the inpatient pharmacy. Dispensing procedures are prepared by the IDS Pharmacist and are included in the IDDS. **Outpatient:** Investigational drugs are dispensed Monday through Friday between 8:30am and 4pm pursuant to the receipt of a legal prescription. Orders may be placed by mail, or fax, and are encouraged to be placed at least 4 days in advance. The IDS will deliver prescriptions to specified locations within the SMH hospital complex.

SPECIAL SERVICES

Special services are available through the IDS and require advanced planning. Contact the IDS Coordinator to discuss the availability and costs associated with the services.

Special Compounding: This may include specially formulated placebo capsules, suspensions, or dosage forms which are not commercially available. The manufacturing area of the Department of Pharmacy may also participate in such studies.

Randomization Schemes: The IDS can prepare randomization schemes to meet the needs of most studies. A statistician should be consulted if other statistical matters need to be addressed in the study design.

Assistance with Protocol Development: The IDS will assist the Principal Investigator in the design of a protocol as it pertains to the pharmacy's role.

EXPLANATION OF IDS FEES

Operational costs associated with the Investigational Drug Service must be planned for in the initial stages of protocol development. These costs are the responsibility of the Principal Investigator and budgetary arrangements must be mutually acceptable and agreed upon by the IDS Coordinator and the Principal Investigator. The IDS Coordinator will provide the Principal Investigator with a written assessment of the Department of Pharmacy's costs associated with the drug study, prior to Institutional Review Board (IRB) review/study initiation, so that these costs can be incorporated into the study budget.

The IDS charges fees to cover the direct costs of providing services to the Principal Investigator. Fees fall into the following categories.

For each study the IDS pharmacist(s) will provide each Investigator a detailed pharmacy budget specific to their study.

Fixed IDS Fees

Start-Up Fee (one time charge at study initiation)

Protocol Review and Set-up

Maintenance Fee (billed monthly)

Charged regardless of patient enrollment
Storage/facilities
Billing
Phone calls

Charged per month
Monthly Inventory
Correspondence

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

[X] NEW application. *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

[ ] COMPETING CONTINUATION of grant number: _____
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl.only)*
[ ] No [ ] Previously reported
[ ] Yes. If "Yes," [ ] Not previously reported

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

[ ] FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

•Human Subjects; •Vertebrate Animals; •Debarment and Suspension; •Drug-Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only);* •Lobbying; •Delinquent Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 19.)*

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
	None	

3. FACILITIES AND ADMINISTRATION COSTS (F & A)

Indicate the applicant organization's most recent F & A cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative F & A cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates,* and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. F & A costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, and specialized grant applications.

[X] DHHS Agreement dated: 7/26/99 [ ] No Facilities and Administration Costs Requested.

[ ] DHHS Agreement being negotiated with _____ Regional Office.

[ ] No DHHS Agreement, but rate established with _____ Date _____

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on F & A costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base $ 109,220 x Rate applied 59.5 % = F & A costs (1) $ 64,986

b. Entire proposed project period: Amount of base $ 572,500 x Rate applied 59.5 % = F & A costs (2) $ 340,638

(1) Add to total direct costs from form page 4 and enter new total on Face Page, Item 7b.
(2) Add to total direct costs from form page 5 and enter new total on Face Page, Item 8b.

*Check appropriate box(es):

[ ] Salary and wages base [X] Modified total direct cost base [ ] Other base *(Explain)*
[ ] Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

4. SMOKE-FREE WORKPLACE

Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?

[X] Yes [ ] No *(The response to this question has no impact on the review or funding of this application.)*

AA

Form Approved Through 2/28/01
OMB No. 0925-0001

Department of Health and Human Services

6 9 1 6 1 6 JUN 11 2000

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

PI: **LAPTOOK, ABBOT**
1 U10 HD040689-01
Dual:
IRG: ZHD1 SRC(99)

Council: 01/2001
Received: 07/11/2000

1. TITLE OF PROJECT: Cooperative Multicenter Neonatal Research Network

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES *(If "Yes," state number and title)*
Number: HD-00-010 Title: Cooperative Multicenter Neonatal Research Network

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — New Investigator ☒ Yes

3a. NAME *(Last, first, middle)*
Laptook, Abbot Roy

3b. DEGREE(S)
B.A., M.D.

3c. SOCIAL SECURITY NO.
Provide on Form Page KK

3d. POSITION TITLE
Prof. of Pediatrics and OB/Gyn

3e. MAILING ADDRESS *(Street, city, state, zip code)*
The University of Texas Southwestern
Medical Center at Dallas
Department of Pediatrics
5323 Harry Hines Boulevard
Dallas, Texas 75390-9063

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Neonatal Pediatrics

3g. MAJOR SUBDIVISION
Southwestern Medical School

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: (214) 648-3753
FAX: (214) 648-2481

E-MAIL ADDRESS:
Alapto@mednet.swmed.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date		4b. Assurance of compliance no.
☐ No			
☒ Yes	June 12, 2000	☒ Full IRB ☐ Expedited Review	M1304-01

5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval Date	5b. Animal welfare assurance no.
☒ No		
☐ Yes		

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
04/01/01	03/31/06	113,861	177,623	603,576	941,579

9. APPLICANT ORGANIZATION
Name UT Southwestern Medical Center @ Dallas
Address Department of Pediatrics
5323 Harry Hines Boulevard
Dallas, Texas 75390-9105

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER
1756002868A4
DUNS NO. *(if available)*
80-077-1545

Congressional District
30

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name Perrie M. Adams, Ph.D.
Title Associate Dean for Research
Address UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390-9105
Telephone (214) 648-5100
FAX (214) 648-5150
E-Mail grants.mgt@email.swmed.edu

14. OFFICIAL SIGNING FOR APPLICATION ORGANIZATION
Name Perrie M. Adams, Ph.D.
Title Associate Dean for Research
Address UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390-9105
Telephone (214) 648-5100
FAX (214) 648-5150
E-Mail grants.mgt@email.swmed.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
Abbot Laptook

DATE
7/7/00

16. APPLICATION ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. . *(In ink. "Per" signature not acceptable.)*
Perrie M Adams

DATE
7/10/00

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This proposal is a reapplication from The University of Texas Southwestern Medical Center at Dallas to participate in the Cooperative Multicenter Neonatal Research Network (RFA: HD-00-010). Abbot R. Laptook, M.D. will serve as the Principal Investigator and the Alternate will be Walid A. Salhab, M.D. The primary teaching hospital of the UT Southwestern Medical Center is Parkland Hospital, which has the largest delivery population of any hospital in the United States. The Neonatal Intensive Care Unit (NICU) at Parkland has a bed capacity of 100 and is a state of the art facility. Adjoining Parkland Hospital is Children's Medical Center, which provides all needed specialized pediatric services for radiologic, operative, and cardiac procedures. There are a number of considerations that justify UT Southwestern continuing as one of the sites for the Network. First, a large inborn population is provided, and in spite of changes in health care delivery, Parkland Health and Hospital System has been able to maintain their delivery population, and admissions to the NICU have been relatively constant over the past decade. This reflects a well organized institutional approach to providing health care, and an established Obstetric service which is integrated within the health care delivery services of targeted communities of Dallas. Second, the UT Southwestern site offers ethnic diversity for the Network by providing a large number of Hispanic patients. Currently, the delivery population is 77% Hispanic and admissions to the NICU are 64% Hispanic. Third, the UT Southwestern site has a proven track record within the Network. It has been a member institution since the inception of the Network and continues to have a well organized system with a high percent of eligible infants enrolled in randomized trials, limited errors in conducting studies, complete data acquisition, and an almost 90% follow-up rate. Fourth, the PI provides expertise in cerebral metabolism and blood flow which will benefit the design and implementation of studies directed at perinatal brain damage. Finally, the Division of Neonatal-Perinatal Medicine at UT Southwestern has a strong commitment to clinical research and maintains a clinical management approach, which is reluctant to adopt new therapies without sufficient evaluation and evidence.

PERFORMANCE SITE(S) (*organization, city, state*)

The University of Texas Southwestern Medical Center
Dallas, Texas

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Abbot R. Laptook, M.D.	UT Southwestern Medical Center	Principal Investigator
Walid A. Salhab, M.D.	UT Southwestern Medical Center	Alternate
Rebecca Sue Broyles, M.D.	UT Southwestern Medical Center	Follow-Up Director
Kenneth J. Leveno, M.D.	UT Southwestern Medical Center	Consultant

RESEARCH GRANT

TABLE OF CONTENTS

*Type density and size must conform to limits provided in Specific Instructions on page 6.

Appendix *(Five collated sets. No page numbering necessary for Appendix.)* [X] Check if Appendix is included

Number of publications and manuscripts accepted or submitted for publication *(not to exceed 10)* 10

Other items (list):

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM 4/01/01 THROUGH 3/31/02

PERSONNEL *(Applicant organization only)* NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Abbot R. Laptook, M.D.	Principal Investigator	#	%	$	16,120 16,250	3063 ~~3,088~~	19183 ~~19,338~~
Walid A. Salhab, M.D.	Co-Investigator				0	0	0
Susie Madison, R.N.	Research Nurse				43,528	9,576	53,104
Clara Alder, R.N.	Research Nurse				21,245	4,674	25,919
SUBTOTALS →					~~81,023~~ 80,893	~~17,338~~ 17313	98,361

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)* Laboratory supplies: syringes, tubes, needles, lancets, foot warming pads	3,000
TRAVEL 6 round trips to Bethesda for Committee meetings for PI @ $1000/trip 4 round trips to Bethesda for Research Nurses @ $1000/trip	10,000
PATIENT CARE COSTS — INPATIENT	
PATIENT CARE COSTS — OUTPATIENT	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Pagers for nursing personnel @ $15./month/nurse (2 Research Nurses, 3 follow-up nurses) = $900 Publication charges = $600 Long distance phone charges = $500 Shipping = $500	2,500
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD	**$ 113,861**
CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS	
CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATION COSTS	
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* →	**$ 113,861**

Number pages consecutively at the bottom throughout the application. Do *not* use suffixes such as 3a, 3b.

= Months Devoted to Project

% = Percentage of Effort

$ = Institutional Based Salary

BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD *(from Form Page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits Applicant organization only*		98,361	101,312	104,351	107,482	110,706
CONSULTANT COSTS		0	0	0	0	0
EQUIPMENT		0	0	0	0	0
SUPPLIES		3,000	3,000	3,000	3,000	3,000
TRAVEL		10,000	10,300	10,609	10,927	11,255
PATIENT CARE COSTS	INPATIENT	0	0	0	0	0
	OUTPATIENT	0	0	0	0	0
ALTERATIONS AND RENOVATIONS		0	0	0	0	0
OTHER EXPENSES		2,500	2,575	2,652	2,732	2,814
SUBTOTAL DIRECT COSTS		113,861	117,187	120,612	124,141	127,775
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
	F&A					
TOTAL DIRECT COSTS		113,861	117,187	120,612	124,141	127,775

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD *(Item 8a, Face Page)* → **603,576**

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Personnel

1. Abbot R. Laptook, M.D.: Dr. Laptook will serve as the PI for the UT-Southwestern site. He has functioned in this capacity since July of 1998 when Dr. Tyson departed and an expanded UT site was created (Houston and Dallas). He has had prior grant support from the National Institutes of Health, American Heart Association and United Cerebral Palsy Foundation. Dr. Laptook will devote % of his time to Network studies but only % of his salary is requested as stipulated by the RFA.

2. Walid A. Salhab, M.D.: Dr. Salhab will function as the alternate for the UT-Southwestern site. He will work closely with Dr. Laptook and the Research Nurses regarding implementation and conduct of studies in the Parkland nurseries. He will be the primary investigator at the UT-Southwestern site for two specific studies (Benchmarking and iNO for the preterm infant). He will dedicate % of his time to Network studies and no salary is requested as per the RFA.

3. Susie Madison, R.N.: Ms. Madison will serve as the UT-Southwestern site Nurse Coordinator and has 6 years experience in this position. She will be responsible for coordinating Network studies including implementing protocols, recruitment of patients, coordinating with ancillary services (Investigational Drug Pharmacy, Respiratory Therapy, Radiology, etc.), data collection and communication with the IRB regarding specific studies. She is also responsible for maintaining the GDB (screening, data collection) and communication with NICHD (conference calls, training sessions, etc.). She will dedicate % of her time to Neonatal studies and her full salary has been requested.

4. Clara Alder, R.N.: Ms. Alder is a Research Nurse who will fulfill the % FTE for data entry. The justification for using a Research Nurse for data entry is to provide greater efficiency for the Network site. The work load is remarkably variable depending upon study status and census; when busy there is unequivocally too much work for a single Research Nurse and having someone with multi-task responsibilities alleviates this burden. In addition, Ms. Alder can cover for the Coordinator when she is sick, on vacation or at a Network meeting in addition to helping with holiday coverage. Ms. Alder has 16 years of Neonatal Intensive Care Nursing experience, at a level III center in Dallas. She will work part-time to provide % of an FTE for her responsibilities and her salary has been requested.

Supplies:

Justification as noted on the detailed budget for 4/1/01 - 3/31/02.

Travel:

Ten trips are requested (six for the PI, four for the Research Nurse) as stipulated by the RFA.

Other Expenses:

Monies are requested for pagers to be used by two Research Nurses and three Pediatric Nurse Practitioners in the Follow-Up Clinic. The beepers are essential for the Research Nurses and allow staff in the Nurseries to contact Network personnel regarding questions about study patients or protocol. As delineated in Section V-C, the success of the follow-up program in this population is contingent upon providing comprehensive care. One of the essential features of the primary care program is that parents can call their specific provider at any time of the day, seven days per week using the beeper system. The beepers for the Follow-Up Clinic Pediatric Nurse Practitioners help achieve an important goal of the Network site.

Other expenses are as delineated on the detailed budget for 4/1/01 - 3/31/02. The budget for years 2 - 5 reflects 3% increases in costs for personnel, travel and other expenses as stipulated by the RFA.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

% = Percentage of Effort

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Abbot R. Laptook, M.D.	Professor of Pediatrics and Obstetric/Gynecology

EDUCATION/TRAINING(*Begin with baccalaureate or other initial professional education, such as nursing, and including postdoctoral training.)*

INSITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Clark University-Worcester, Mass	B.A.	1972	Biology
State University of New York, Downstate Medical Center, Brooklyn, N.Y.	M.D.	1976	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1976-1977 Intern, Pediatrics, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY
1977-1979 Resident, Pediatrics, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY
1979-1981 Postdoctoral Fellow, Division of Neonatology, Women and Infants Hospital of Rhode Island, Providence, RI
1981-1988 Assistant Professor of Pediatrics and Obstetrics/Gynecology, UT-Southwestern Medical Center, Dallas, TX
1988-1995 Associate Professor of Pediatrics and Obstetrics/Gynecology, UT-Southwestern Medical Center, Dallas, TX
1995-present Professor of Pediatrics and Obstetrics/Gynecology, UT-Southwestern Medical Center, Dallas, TX

HONORS

1972 Phi Beta Kappa, Clark University
1977 Samuel Karelitz Intern of the Year, Long Island Jewish-Hillside Medical Center
1979 Pediatric Neurology Award, Long Island Jewish-Hillside Medical Center
1976-1979 Most Outstanding House Staff Member, Long Island Jewish-Hillside Medical Center
1984 Faculty Teaching Award, Children's Medical Center, Dallas, Texas

PUBLICATIONS: (30 of 65 publications)

1. Laptook AR, Corbett RJT, Uauy R, Mize C, Mendelsohn D, and Nunnally RL: Use of P-31 magnetic resonance spectroscopy to characterize evolving brain damage after perinatal asphyxia. Neurology 39:709-719, 1989.
2. Corbett RJT, Laptook AR, and Olivares E: Simultaneous measurement of cerebral blood flow and energy metabolites in piglets using deuterium and phosphorus nuclear magnetic resonance. J. Cereb. Blood Flow Metabol. 11:55-65,1991.
3. Corbett RJT, Laptook AR, Ruley JR, and Garcia D: The effect of age on the glucose modulated cerebral agonal glycolytic rates measured in vivo by ^{1}H NMR spectroscopy. Pediatr. Res. 30:579-586,1991.
4. Laptook AR, Corbett RJT, Ruley J, and Olivares E: Blood flow and metabolism during and following repeated partial brain ischemia in neonatal piglets. Stroke 23:380-387,1992.
5. Corbett RJT, Laptook AR, Garcia D, and Ruley J: Cerebral acid buffering capacity at different ages measured in vivo by ^{31}P and ^{1}H nuclear magnetic resonance spectroscopy. J. Neurochem. 59:216-226,1992.
6. Laptook AR, Corbett RJT, Arencibia-Mireles O, and Ruley J: Glucose associated alterations in ischemic brain metabolism of neonatal piglets. Stroke 23:1504-1511,1992.
7. Corbett RJT, Laptook AR, Garcia D, and Ruley J: Energy reserves and utilization rates in developing brain measured in vivo by ^{31}P and ^{1}H nuclear magnetic resonance spectroscopy. J. Cereb. Blood Flow Metabol. 13:235-246,1993.
8. Corbett RJT and Laptook AR: ^{31}P NMR relaxation does not effect the quantitation of changes in phosphocreatine, inorganic phosphate, and ATP measured in vivo during complete ischemia in swine brain. J. Neurochem. 61:144-149,1993.
9. Corbett RJT, Laptook AR, Sterett R. Tollefsbol G and Garcia D: The effect of hypercarbia on age related changes in cerebral glucose transport and glucose modulated agonal glycolytic rates. Pediatr. Res. 34:370-378,1993.
10. Laptook AR, Corbett RJT, Arencibia-Mireles O, Ruley J and Garcia D: The effects of systemic glucose concentration on brain metabolism following repeated brain ischemia. Brain Res. 638:78-84,1994.

11. Laptook AR, Corbett RJT, Sterett R, Burns DK, Tollefsbol G, and Garcia D: Modest hypothermia provides partial neuroprotection for ischemic neonatal brain. Pediatr. Res. 35:436-442,1994.
12. Corbett RJT, Laptook AR, Tollefsbol G and Kim B: Validation of a noninvasive method to measure brain temperature in vivo using ^{1}H NMR spectroscopy. J. Neurochem. 64:1224-1230,1995
13. King TA, Perlman JM, Laptook AR, Rollins N, Jackson G, and Little B: Neurologic manifestations of in-utero cocaine exposure in near-term and term infants. Pediatrics. 96:259-264,1995.
14. Laptook AR, Corbett RJT, Sterett R, Garcia D, and Tollefsbol G: Quantitative relationship between brain temperature and energy utilization rate measured in-vivo using ^{31}P and ^{1}H magnetic resonance spectroscopy. Pediatr. Res. 38:919-925,1995.
15. Laptook AR, Corbett RJT, Burns D, Sterett R: Neonatal ischemic neuroprotection by modest hypothermia is associated with attenuated brain acidosis. Stroke 26:1240-1246,1995.
16. Corbett RJT, Laptook AR, Sterett R, Tollefsbol G, Garcia D: Effect of hypoxia on glucose-modulated cerebral lactic acidosis, agonal glycolytic rates, and energy utilization. Pediatr. Res. 39:477-486,1996.
17. Corbett RJT, Gee J, Laptook AR: Calculation of intracellular cerebral [Mg^{2+}] during hypoxia-ischemia by in vivo ^{31}P NMR. NeuroReport 8:287-291,1996.
18. Laptook AR, Corbett RJT, Sterett R, Burns DK, Garcia D, Tollefsbol G: Modest hypothermia provides partial neuroprotection when used for immediate resuscitation following brain ischemia. Pediatr. Res. 42:1-7,1997.
19. Corbett RJ, Laptook A, Weatherall P: Noninvasive measurement of human brain temperature using volume localized proton magnetic resonance spectroscopy. J Cereb. Blood Flow Metabol. 17:363-369,1997.
20. King TA, Jackson GL, Josey S, Vedro DA, Hawkins H, Burton KM, Burks MN, Yellin WM, Laptook AR: The effect of profound umbilical artery acidemia in term neonates admitted to a newborn nursery. J Pediatr 132:624-629,1998.
21. Corbett RJT and Laptook AR: Failure of localized head cooling to reduce brain temperature in adult humans. NeuroReport 9:2721-2725,1998.
22. Corbett R, Laptook A, Gee J, Garcia D, Silmon S, Tollefsbol G: Age related differences in the effect of dichloroacetate on postischemic lactate and acid clearance measured in vivo using magnetic resonance spectroscopy and microdialysis. J Neurochem 71,1205-1214,1998.
23. Corbett R, Laptook A, Kim B, Tollefsbol G, Silmon S, Garcia D: Maturational changes in cerebral lactate and acid clearance following ischemia measured *in vivo* using magnetic resonance spectroscopy and microdialysis. Develop Brain Res 113:37-46,1999.
24. Corbett R, Batista A, Laptook A, Sherry A: A macrocyclic reporter ligand for Mg^{2+}: Analytical implications for clinical magnesium determinations. Magnesium Research 12:79-88,1999.
25. Engle WD, Laptook AR, Perlman JM: Acute changes in arterial carbon dioxide tension and acid-base status and early neurologic characteristics in term infants following perinatal asphyxia. Resuscitation 42:11-17, 1999.
26. Corbett RJT, Purdy PD, Laptook AR, Chaney C, Garcia D: Noninvasive measurement of brain temperature after stroke. Am. J. Neuroradiol. 20:1851-1857, 1999.
27. Gee JB, Corbett RJT, Perlman JM, Garcia D, Laptook AR: Age dependent differences in the relationship between plasma and brain extracellular fluid concentrations of magnesium after $MgSO_4$ infusions in miniswine. Pediatr. Res. 46:281-286, 1999.
28. Laptook AR, Corbett RJT, Burns DK, Sterett R: A limited interval of delayed modest hypothermia for ischemic brain resuscitation is not beneficial in neonatal swine. Pediatr. Res. 46:383-389, 1999.
29. Batista A, Corbett R, Tidor S, Castleman E, Laptook A, Sherry D: Comparison of the distribution of magnesium in plasma determined by size exclusion chromatography and ^{31}P NMR spectroscopy. Magnesium Res. 13:3-9, 2000.
30. Pending Publication

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Walid Antoun Salhab, M.D.	Assistant Professor of Pediatrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
American University of Beirut, School of Arts and Sciences, Beirut, Lebanon	B.S.	1985-1988	Biology
American University of Beirut, School of Medicine, Beirut, Lebanon	M.D.	1988-1992	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1992-1993 Pediatric Internship, University of Tennessee, LeBonheur Children's Hospital, Memphis, Tennessee
1993-1995 Pediatric Residency, University of Tennessee, LeBonheur Children's Hospital, Memphis, Tennessee
1995-1998 Postdoctoral Fellowship, UT-Southwestern Medical Center, Dallas, Texas
1998-Present Assistant Professor of Pediatrics, UT-Southwestern Medical Center, Dallas, Texas

HONORS:

Spring 1986 - Spring 1988 - Dean's Honor List, American University of Beirut, Beirut, Lebanon
1997 - President's Presenter Award by the Society for Gynecologic Investigation, San Diego, California
1999 - Young Investigator Award by the American Academy of Pediatrics, Section on Perinatal Pediatrics, October, 1999, Washington, D.C.

PUBLICATIONS:

1. Ward, D.G., Wang, W., Fesmire, W., and Salhab, W. A deep-tissue hemangioma presenting as a rapidly progressive expanding mass and thrombocytopenia in an infant. Pediatr Emerg Care 12:422-424, 1996.

2. Salhab, W.A., Shaul, P.W., Cox, B.E., and Rosenfeld, C.R. Regulation of types I and III NOS in ovine uterine arteries by daily and acute estrogen exposure. Am J Physiol Heart Circ Physiol 278:H2134 - H2142, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Rebecca Sue Broyles, M.D.	Assistant Professor of Pediatrics

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Stephen F. Austin State University, Nacogdoches, Texas		1972-73	Zoology
University of Texas - Austin, Texas	B.S.	1976	Biology/Zoology
University of Texas Medical Branch - Galveston, Texas	M.D.	1982	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1982-1985 Pediatric Internship and Pediatric Residency, Children's Medical Center, Dallas, Texas
1988-1991 Neonatology Fellowship, UT-Southwestern Medical Center, Dallas, Texas
1991-Present Assistant Professor of Pediatrics, UT-Southwestern Medical Center; Medical Director, Low Birth Weight Clinic, Children's Medical Center, Dallas, Texas

HONORS:

1976 Summa Cum Laude, University of Texas, Austin, Texas
1976 Alpha Epsilon Delta, University of Texas, Austin, Texas
1985 Award for Outstanding Resident by ICU Staff (Jaws Award)

PUBLICATIONS:

1. Broyles S, Sharp C, Tyson J, Sadler J. How should parents be informed about major procedures: An exploratory trial in the neonatal period. Early Hum. Develop. 31:67-75, 1992.

2. Tyson J, Kennedy K, Broyles S, Rosenfeld C. The small for gestational age infant: accelerated or delayed pulmonary maturity? Increased or decreased survival. Pediatrics 95(4):534-538, 1995.

3. Perlman JM, Risser R, Broyles RS. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. Pediatrics 97(6 Pt 1):822-827, 1996.

4. Tyson J, Broyles RS. Progress in assessing the long-term outcome of extremely low-birth-weight infants. JAMA 276(6):492-493, 1996.

5. Broyles RS, Tyson JE, Swint JM. Have Medicaid reimbursements been a credible measure of the cost of pediatric care? Pediatrics 99(3):E8, 1997.

6. Hoffman C, Broyles RS, Tyson JE. Emergency room visits despite the availability of primary care: A study of high risk inner city infants. American Journal of the Medical Sciences. 313(2):99-103, 1997.

7. McCarton CM, Brooks-Gunn J, Wallace IF, Bauer CR, Bennett FC, Bernbaum JC, Broyles RS, Casey PH, McCormick MC, Scott DT, Tyson J, Tonascia J, Meinert CL for the Infant Health and Development Program Research Group. Results at age 8 years of early intervention for low-birth-weight premature infants. JAMA. 277(2):126-132, 1997.

8. Perlman JM, Broyles RS, Rogers CG. Neonatal neurologic characteristics of preterm twin infants <1,250gm birth weight. Pediatric Neurology. 17(4):322-326, 1997.

9. Rogers CG, Tyson JE, Kennedy KA, Broyles RS, Hickman JF. Conventional consent with opting in versus simplified consent with opting out: an exploratory trial for studies that do not increase patient risk. Journal of Pediatrics. 132(4):606-611, 1998.

10. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, Simon NP, Wilson DC, Broyles S, Bauer Cr, Delaney-Black V, Yolton KA, Fleisher BE, Papile LA, Kaplan MD. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics. 105(6):1216-26, June 2000.

11. Broyles RS, Tyson JE, Heyne ET, Hickman JF, Swint M, Adams SS, West LA, Pomeroy N, Hicks PJ, Ahn C: Access to comprehensive follow-up care reduces life-threatening illnesses among high risk inner-city infants. Submitted to JAMA, 2000.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Kenneth J. Leveno, M.D.	Professor and Chief of Obstetrics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE (If applicable)	YEAR(s)	FIELD OF STUDY
University of Notre Dame, South Bend, IN	B.S.	1960-1964	Pre-professional Studies
Creighton School of Medicine, Omaha, NE	M.D.	1964-1968	Medicine
Creighton School of Medicine, Omaha, NE	Internship	1968-1969	General Surgery
St. Joseph Hospital, Phoenix, AZ	Residency	1973-1976	Obstetrics & Gynecology
UT Southwestern Medical Center, Dallas, TX	Fellowship	1976-1978	Maternal-Fetal Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1969-1973 U.S. Army Medical Corps
1978-1984 Assistant Professor, Dept. of Obstetrics & Gynecology, UT Southwestern Medical Center, Dallas, TX.
1980-1988 Co-Director, High Risk Pregnancy Unit, Parkland Memorial Hospital, Dallas, TX.
1984-1988 Associate Professor, Dept. of Obstetrics & Gynecology, UT Southwestern Medical Center, Dallas, TX.
1984-Present Chief of Obstetrics, Parkland Memorial Hospital, Dallas, TX.
1988-Present Professor, Department of Obstetrics & Gynecology, UT Southwestern Medical Center, Dallas, TX.
1990-Present Gillette Professor of Obstetrics, Dept. of Obstetrics & Gynecology, UT Southwestern Medical Center, Dallas, TX.
1996-Present Director, Maternal-Fetal Medicine, Dept. of Obstetrics & Gynecology, UT Southwestern Medical Center, Dallas, TX.

HONORS: Resident Teaching Award, Parkland Memorial Hospital, 1984, 1993, and 1994; National Faculty Award, Excellence in Resident Education, CREOG, 1994; Certification: American Board of Obstetrics and Gynecology, 1981 and 1989; Maternal-Fetal Medicine, 1983. Distinguished Physician Award, Parkland Memorial Hospital, 1998.

Selected Representative Publications (From 190 citations)

Leveno KJ, Quirk JG, Jr., Cunningham FG, Nelson SD, Santos-Ramos S, Toofanian A., DePalma RT: Prolonged pregnancy. I. Observations concerning the causes of fetal distress. *Am J Obstet Gynecol* 150:465-73, 1984.

Leveno KJ, Cunningham FG: Beta-adrenergic agonists for preterm labor. *N Engl J Med* 327:349-351, 1992.

Nathan L, Leveno KJ, Carmody, TJ, III, Kelly MA, Sherman ML: Meconium: a 1990s perspective on an old obstetric hazard. *Obstet Gynecol* 83:329-332, 1994.

Satin, AJ, Leveno KJ, Sherman ML, McIntire D: High dose oxytocin: 20 versus 40 minute dosage intervals. *Obstet Gynecol* 83:234-238, 1994.

Cunningham FG, Leveno KJ: Childbearing among older women – the message is cautiously optimistic. [editorial] *N Engl J Med* 333:1002-1004, 1995.

Lucas MJ, Leveno KJ, Cunningham FG: A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 333:201-205, 1995.

Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG: Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 87:487-494, 1997.

Casey BM, Lucas MJ, McIntire DD, Leveno KJ: Pregnancy outcomes in women with gestational diabetes compared to the general obstetrical population. *Obstet Gynecol* 90:869-873, 1997.

Leveno KJ, Letter to the editor. Reply Mittendorf et al, Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 351:291-292, 1998.

Alexander JM, Lucas MJ, Ramin SM, McIntire DD, Leveno KJ: The course of labor with and without epidural analgesia. *Am J Obstet Gynecol* 178:516-520, 1998.

Leveno KJ, Alexander JM, McIntire DD, Lucas MJ: Does magnesium sulfate given for prevention of eclampsia affect the outcome of labor? *Am J Obstet Gynecol* 178:707-712, 1998.

Alexander JM, Gilstrap LC, Cox SM, McIntire DD, Leveno KJ: Clinical chorioamnionitis for very low-birthweight infants. *Obstet Gynecol* 91:725-729, 1998.

Bloom SL, McIntire DD, Kelly MA, Beimer HL, Burpo RH, Garcia MA, Leveno KJ: Lack of the effect of walking on active labor. *N Engl J Med* 339:76-79, 1998.

McIntire DD, Bloom SL, Casey BM, Leveno KJ: Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med, 340:1234-8. 1999.

Hollier, L.M., McIntire, D.D., Leveno, K.J.: Outcome of twin pregnancies according to intrapair birthweight differences. Obstet. Gynecol. 94:1006-10, 1999.

Alexander, J.M., McIntire, D.D., Leveno, K.J.: Chorioamnionitis and the prognosis for term infants. Obstet Gynecol. 94:274-8, 1999.

Carey, J.C., Klebanoff, M.A., Hauth, J.C., Hillier, S.L., Thom, E.A., Ernest, J.M., Heine, R.P., Nugent, R.P., Fischer, M.L., Leveno, K.J., Wapner, R., Varner, M., and the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Metronidazole to prevent preterm birth among asymptomatic pregnant women with bacterial vaginosis. N. Engl. J. Med 342:534-40,2000.

Casey, B.M., McIntire, D.D., Bloom, S.L., Lucas, M.J., Santos, R., Twickler, D.M., Ramus, R.M., Leveno, K.J.: Pregnancy outcomes after antepartum diagnosis of oligohydramnios at or beyond 34 weeks gestation. Am. J. Obstet. Gynecol. 182:909-12, 2000.

Dashe, J., Nathan, L., Leveno, K.J., Lucas, M.J., McIntire, D.D., Kelly, M.A.: Amnionic fluid volume and glucose concentration in pregnancy complicated by diabetes. Am. J. Obstet. Gynecol., 182:901-4, 2000.

Pending Publication

Pending Publication

Wendel, G.D., McIntire, D.J., Leveno, K.J.: Letter to the editor. Reducing neonatal Group B Streptococcal disease. N. Engl. J. Med. 342:1367-8, 2000.

Pending Publication

Other Support

LAPTOOK, A.R.

ACTIVE

No. 5-U10-HD21373-15 (Laptook) 4/1/96 - 3/31/01 %
NIH/NICHD $154,659.00
MultiCenter Network of Neonatal Intensive Care Units

The major goal is to investigate the safety and efficacy of treatment and management strategies to care for newborn infants, especially premature infants.

PENDING

None

OVERLAP

None

SALHAB, W.A.

ACTIVE

(Perlman) 3/3/2000 - 12/3/2000 %
Private Support $4,000/patient enrolled
Surfaxin® vs. standard care in Meconium Aspiration Syndrome (MAS)

The major goals of this project are to demonstrate the safety and efficacy of an exogenous synthetic pulmonary surfactant, Surfaxin®, when administered by bronchoalveolar lavage in the treatment of MAS in newborn infants.

PENDING

None

OVERLAP

None

BROYLES, R.S.

ACTIVE

(Broyles) 9/1/98 - %
Private Support $9,816.59
The Effects of a Formula Supplemented with LC-PUFA on Growth and Development in Preterm Infants

The major goals of this study are to assess the effects of preterm formula supplemented with LC-PUFA on growth and development.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

% = Percentage of Effort

Other Support (Continued)

ROI HD 34116-03 (Leveno) 4/1/98 - %
NIH $30,180.00
Beneficial Effects of Antenatal Magnesium

The major goals of this study are to assess the effect of antenatal treatment with magnesium sulfate on the incidence of cerebral palsy in infants born to women with preterm labor.

PENDING
None

OVERLAP
None

LEVENO, K.J.

ACTIVE

No. 5-U10-HD34116 (Leveno) 5/5/96 - 3/31/01 %
National Institutes of Health $1,891,171.00
Cooperative Multicenter Maternal-Fetal
Medicine Unit Network

The goal is to participate in the NICHD multicenter network of maternal-fetal medicine units and to conduct studies approved, implemented, and supported by the network.

No. 1-R01-HD38663-01 (Leveno) 9/30/99 - 9/30/04 %
National Institutes of Health $1,230,442.00
Childbirth Related Pelvic Floor Injury

The goal is to investigate obstetric antecedents to childbirth related pelvic floor injury.

No. 2-P01-HD11149-21 (Mendelson, Program Dir.) 4/1/98 - 3/31/03
National Institutes of Health $5,331,541.00
Initiation of Human Labor: Prevention of Prematurity
Tissue Laboratory Core A (Leveno) $ 153,184.00 %

The goals of this project are to provide tissues and cells in culture to projects of this Program-Project research program.

PENDING
None

OVERLAP
None

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

% = Percentage of Effort

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory: All laboratory facilities necessary for the conduct of clinical studies are available at Parkland Hospital. This includes laboratory facilities to assess general chemistry values, hematologic values, immunologic and bacteriologic data. In addition, the laboratory of the Principal Investigator provides the Network Research Nurse space and equipment to process and store samples of blood or other body fluids.

Clinical: The Neonatal Intensive Care Unit at Parkland Hospital has a 100 bed capacity and is a state of the art facility for the care of premature newborns and critically ill term infants. Ancillary support services within the NICU include Radiology, Pharmacy and Respiratory Therapy. Specialized radiologic services, interventional cardiology and operating suites are available at Children's Medical Center which adjoins Parkland Hospital.

Animal: Not applicable.

Computer: A micron pentium computer, purchased with Network funds, is dedicated for the Network Research staff to interface with the Data Coordinating Center. The Department of Pediatrics provides computers to all faculty with access to the Internet to enhance communication within and between other universiteis.

Office: The Division of Neonatal - Perinatal Medicine provides office space for the PI, the Alternate and all research staff of the Network. In addition, there is dedicated work areas in the NICU at Parkland Hospital for the Network research staff, and space to store equipment for Network studies.

Other: UT-Southwestern provides a complete environment to support the needs of researchers. Additional support services include medical illustration and biomedical engineering.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Not applicable

This proposal is a reapplication from the University of Texas Southwestern Medical Center at Dallas to participate in the Cooperative Multicenter Neonatal Research Network sponsored by the National Institute of Child Health and Human Development (RFA: HD-00-010). The UT-Southwestern site has been a member of the Network since its inception and the Principle Investigator (PI) has been Jon Tyson, M.D. with Kathleen Kennedy M.D. as the alternate. In July of 1998 Drs. Tyson and Kennedy moved to the University of Texas at Houston, and for the remainder of the current award cycle Dr. Tyson has served as the PI for an expanded University of Texas site incorporating both the Dallas and Houston centers. For the present reapplication Abbot Laptook, M.D. will serve as the PI and the Alternate will be Walid Salhab, M.D. Dr. Laptook is Professor of Pediatrics and Obstetrics and Gynecology at the University of Texas Southwestern Medical Center and his qualifications are discussed below. Dr. Salhab is Assistant Professor of Pediatrics and has been a member of the Division of Neonatal-Perinatal Medicine since October 1998. Dr. Salhab's interest is pulmonary disease processes such as chronic lung disease in the preterm infant and meconium aspiration syndrome in the term infant. He currently oversees the division's extensive data base formerly performed by Dr. Kennedy, is involved in a clinical trial of Surfaxin for infants with meconium aspiration syndrome, and serves as an alternate investigator for the current Network hypothermia protocol. He has worked closely with Dr. Laptook for the past year and has clearly focused his research endeavors on clinical trials.

The UT-Southwestern site owes a tremendous debt of gratitude to Dr. Tyson for his outstanding work in making this center a productive member of the Network for the past 14 years. During his tenure at UT-Southwestern, Dr. Tyson developed extensive experience in multicenter trials, unparalleled expertise in experimental design, and a keen interest in outcomes research. He developed the Follow-up clinic knowing that one of the most important outcomes for any study will ultimately be the neurodevelopmental status during early childhood. He developed a course in Evidence Based Medicine for our Fellows and Faculty which he still conducts jointly between the two institutions via tele-conference. Dr. Salhab has become the faculty member in charge of this course in Dallas and as such works closely with Dr. Tyson to accomplish the objectives. Since Dr. Tyson's departure, Dr. Laptook has served as the PI for the UT-Southwestern site and has worked closely with Dr. Tyson in his role as PI for the expanded UT site. As will be demonstrated below, Dr. Laptook has been extremely diligent in seeing that Network studies are well performed at UT-Southwestern. During the past two years Dr. Laptook's involvement in the Network and his collaborative working relationship with Dr. Tyson have helped Dr. Laptook make a transition from primarily a laboratory based investigator to one who can make important contributions to clinical trials (see Section I-C and letter of reference from Dr. Tyson).

I. ACADEMIC PRODUCTIVITY

A. Qualifications of the PI for the Network:

Dr. Laptook has a background in perinatal research which differs from most of the other PI's in the Network. For the past 19 years, Dr. Laptook's research efforts have been laboratory based and have focused on important issues regarding ischemic brain metabolism and cerebral blood flow using a newborn animal model. A close collaborative relationship was developed with Dr. Ron Corbett in the Department of Radiology at UT-Southwestern and provided a setting to integrate physiologic and biochemical analysis with new technologies of magnetic resonance spectroscopy and imaging. A detailed summary of Dr. Laptook's research is provided in Section II-A. Dr. Laptook's experience in perinatal brain research should be of benefit to the Network objectives. As pointed out in a recent editorial by Dr. Jerold Lucey, "perinatal brain damage ... is the most important, unsolved, neglected problem in neonatology"(1). The current hypothermia protocol represents the first attempt by the Network to study hypoxic-ischemic encephalopathy in the term infant. Given the encouraging laboratory based studies of other potential neuroprotective therapies(2), further study of hypoxic-ischemic encephalopathy should be anticipated for the next funding cycle. Dr. Laptook's expertise and background should be helpful for the design, implementation and conduct of these studies.

B. Participation in Network Research

The following table lists the contribution of patients at the UT-Southwestern center to Network studies during the current award interval (April 1996-May 31, 2000).

CONTRIBUTION OF UT-SOUTHWESTERN PATIENTS TO NETWORK STUDIES

Randomized Trials	Eligible Patients (n)	Enrolled Patients (n)	Proportion of Eligible Patients Enrolled (%)
Vitamin A	53	45	85
TIPP	55	31	56
SAVE	18	15	83
INO	16	15	94
Hypothermia (pilot)	5	4	80
Glutamine	34	26	76

Non-Randomized Entry

GDB		940	
Mg Observational		111	
Follow-up		219	

Dr. Laptook was responsible for the conduct of studies either ongoing (SAVE) or initiated after the departure of Dr. Tyson in July 1998 (iNO, Hypothermia, Glutamine). The high proportion of eligible patients enrolled in randomized trials supports the contention that UT-Southwestern is dedicated to performing quality clinical research in an exemplary fashion. Furthermore, the success of the UT-Southwestern center personnel in achieving patient enrollment has continued under the direction of Dr. Laptook. Additional specific information regarding recruitment and patient characteristics within each randomized trial and nonrandomized entry into the GDB and Follow-up is reviewed below. The following definitions will apply: Hispanic = Hispanic, Black = Black, not of Hispanic Origin, White = White, not of Hispanic Origin.

Vitamin A Trial:

Screened (n)	Ineligible (n)	Eligible, Not Enrolled (n)
104	51	8

Screening was based upon birth weight less than or equal to 1000gm. During this award interval, 4/96 - 3/01, ineligible infants included 31 neonatal deaths before 12 hours of age, 6 neonatal deaths within the first 72 hours of age, 10 infants without need for mechanical ventilation or O_2, 2 infants with congenital malformations and 2 infants with congenital infections (syphilis and one HIV positive mother). Eligible infants not enrolled were due to refusal of consent in 7 (parental refusal n = 6, Attending Physician refusal n = 1) and one mother was unavailable for consent due to her medical condition (postpartum seizures). This investigation spanned two award intervals (4/91 - 3/96 and 4/96 - 3/01), and recruitment occurred between 11/1/95 until 6/3/97. For the entire study period 167 infants were screened, 86 were ineligible, 12 were eligible but not enrolled, and 69 infants were enrolled. The UT-Southwestern center had the highest proportion of eligible patients enrolled for the Vitamin A trial of all Network centers.

The following table lists demographic characteristics for enrolled patients:

	Hispanic	Black	White	Total
Female	15	19	1	35
Male	22	10	2	34
Total	37	29	3	69

TIPP Trial:

Screened (n)	Ineligible (n)	Eligible, Not Enrolled (n)
88	33	24

Screening was based upon birth weight ≤ 1000gm. Ineligible infants included 24 infants who expired and did not receive full intensive care treatment, five infants whose mothers abused illicit drugs and would not be compliant with follow-up, one infant whose mother was visiting from Mexico and could not commit to follow-up, 1 infant with a congenital malformation, 1 infant with thrombocytopenia, and 1 transferred infant in which the time of arrival did not allow time for enrollment. Eligible infants not enrolled included 10 infants in which the Attending refused enrollment (most infants were cardiovascularly unstable), 7 infants in which enrollment could not be achieved in the 6 hour time interval following birth, 4 infants in whom the parents refused consent, and 3 infants in whom informed consent could not be obtained (mother heavily sedated, n = 2, mother with postpartum seizure, n = 1).

The following table lists demographic characteristics for enrolled patients:

	Hispanic	Black	White	Total
Female	5	2	1	8
Male	9	12	2	23
Total	14	14	3	31

SAVE Trial:

Screened (n)	Ineligible (n)	Eligible, Not Enrolled (n)
26	8	3

Screening was based upon birth weight ≤ 1000gm. Ineligible infants included five neonatal deaths before 12 hours of age and three infants with a birth weight > 750gm who did not require surfactant replacement. Eligible infants not enrolled included one parental refusal, one Attending Physician refusal and one parent who was unavailable. The SAVE trial was conducted during the transition from Dr. Tyson to Dr. Laptook. The transition delayed initiation of recruitment into the pilot phase and all patients were enrolled into the pilot after Dr. Tyson's departure. In spite of the transition, the UT-Southwestern site was able to enroll comparable numbers of infants into the main trial compared to other centers.

The following table lists demographic characteristics for enrolled patients in both the pilot (n = 9) and the main trial (n = 6):

	Hispanic	Black	White	Total
Female	3	4	1	8
Male	4	3	0	7
Total	7	7	1	15

Inhaled NO:

Screening for eligible infants for the iNO trial was a more difficult challenge compared to studies with a well defined characterizing feature (e.g. BW ≤ 1000gm). Screening was based upon infants with a gestational age ≥ 34 weeks and requiring mechanical ventilation (n = 94). No statistics are available regarding the number of infants with an OI > 12 (i.e. an infant approaching entry criteria) but ventilator requirements and inspired O_2 concentration of infants ≥ 34 weeks gestation were examined daily. The one eligible infant not enrolled was early in the study (Dec. 1998) when it was not appreciated that once the oxygenation index (OI) was greater than 25, further intensive medical management could be instituted to try to lower the OI into the 15 - 25 range.

The following table lists demographic characteristics for enrolled patients:

	Hispanic	Black	White	Total
Female	6	2	0	8
Male	2	4	1	7
Total	8	6	1	15

Hyperthermia Trial:

Screened (n)	Ineligible (n)	Eligible, Not Enrolled (n)
21	16	1

Screening was based upon the presence of fetal acidemia, or birth depression requiring intubation at birth. Ineligible infants included 12 infants with fetal or neonatal (< 1 hour of age) acidemia but a non-qualifying exam, 2 infants with birth depression (need for intubation/low apgars) but absence of a perinatal event, and 2 infants with seizures but absence of fetal acidemia and birth depression. One infant was eligible but not enrolled due to extreme instability and inability to stabilize by 6 hours of age thus preventing evaluation for the study.

The following table lists demographic characteristics for enrolled patients:

	Hispanic	Black	Total
Male	3	1	4

Glutamine Trial:

Screened (n)	Ineligible (n)	Eligible, Not Enrolled (n)
51	17	8

Infants were screened based upon a birth weight < 1000gm. Ineligible infants included 13 neonatal deaths prior to evaluation for the study, 2 infants with congenital malformations, and 2 infants born to mothers who are HIV positive. Eligible infants not enrolled were due to parental refusal (n = 5) and death prior to randomization (n = 3).

The following table lists demographic characteristics for enrolled patients:

	Hispanic	Black	White	Total
Female	8	6	1	15
Male	4	5	2	11
Total	12	11	3	26

Based upon the above summary of each study, the system used at UT-Southwestern to screen for potential eligibility, establish eligibility, and approach the mother for informed consent is comprehensive, thorough and highly successful.

Generic Data Base:

Entry of patients into the GDB reveals the following number of infants by year of the current award (PH = Parkland Hospital, SPMC = St. Paul Medical Center):

4/1/96 - 3/31/97	4/1/97 - 3/31/98	4/1/98 - 3/31/99	4/1/99 - 3/31/00	4/1/00 - 6/1/00

PH (n)	213	185	224	196	37
SPMC(n)	53	32			

Dr. Tyson decided not to collect data from SPMC as of 12/31/97 due to impending changes at the hospital. The Neonatal service at SPMC was subsequently taken over by another Neonatology group in July 1998. In spite of this change, the entry of patients into the GDB at Parkland Hospital has been reasonably stable with numbers fluctuating within 10% from an average of 205 infants/year for each of the 4 years of the current award. The demographics for patients entered into the GDB is listed in the following table:

	Hispanic	Black	White	Other	Total
Female	204	172	43	10	429
Male	262	192	42	12	508
Ambiguous	0	0	2	1	3
Total	466	364	87	23	940

Follow-up:

Within the current award interval (4/1/96-6/1/00), 219 infants have completed their neurodevelopmental assessment at 18-months corrected age. The demographic characteristics for this group of infants are listed in the following Table:

	Hispanic	Black	White	Other	Total
Female	39	53	7	3	102
Male	43	57	6	11	117
Total	82	110	13	14	219

C. Contribution as a Subcommittee Member:

Dr. Laptook's role as a subcommittee member has been limited since his position has been somewhat unique relative to other PI's. Since Dr. Tyson was serving as the PI for the expanded UT site (Dallas and Houston) it was felt that Dr. Laptook should not have all the responsibilities of a PI, but serve an intermediate role. Given his background, Dr. Laptook's subcommittee role was dedicated to the Hypothermia Protocol. Dr. Laptook played an important role on this subcommittee including 1) providing important contributions in changing the design of the hypothermia trial from one which used head cooling to a study of body cooling after the collaboration with Olympic Biomedical was terminated, 2) performed 6 pilot animal studies to evaluate the Blanketrol Hyper-hypothermia system as a means of inducing whole body cooling and controlling body temperature during body cooling, 3) created a video to facilitate the instruction of all Nurse Coordinators and PI's in the Network regarding the proper use of the Blanketrol system, 4) researched and evaluated alternative temperature probes for monitoring skin and esophageal temperature of infants in the normothermic control group, and 5) assisted Dr. Shankaran in writing specific portions of the protocol (neurologic evaluation, adverse side effects, etc.) and manual (use of the Blanketrol system). The work on evaluation of the Blanketrol system for control of body temperature and consequent effects on brain temperature has led to a manuscript which is currently under internal review within the Network and is included in the Appendix.

During the two years that Dr. Laptook worked with Dr. Tyson and served as the PI for the UT- Southwestern site, he attended all Steering Committee meetings and sat in on all subcommittee sessions for trials ongoing or planned for his site. This participation was essential for efficient and accurate implementation of studies.

D. Participation in Clinical Research Outside the Network

The UT-Southwestern site is participating in a randomized multicenter trial of elective intubation for single dose surfactant treatment in neonates with mild to moderate RDS. The primary objective is to determine whether elective intubation, before it is otherwise required, followed by a single dose of surfactant and then extubation decreases the duration of mechanical ventilation compared to usual management of RDS in the study population. The primary eligibility criteria are gestational age $\leq$ 36 weeks, birth weight $\geq$ 1250gms, 4-24 hours postnatal age, chest x-ray consistent with RDS, $FiO_2 \geq .4$ with or without nasal CPAP for at least one hour, and no requirement for intubation or surfactant replacement therapy. This trial is being performed among academic centers within Texas in an attempt to stimulate clinical research among all university groups within the state and distinguish themselves from private practice groups. Other participating university sites are UT-Galveston, Houston and San Antonio and Texas Tech-Amarillo and El-Paso. This study was designed before the current Network trial regarding CPAP/Surfactant and Dr. Kennedy was involved in the initial planning phase. Since her departure to Houston, Dr Pablo Sanchez is the site PI. The trial is partially supported by Ross Laboratories. The Division at UT-Southwestern felt that the study was similar to the Network trial, that only one study on this topic should be ongoing in the NICU, and that UT-Southwestern should honor its original commitment to the Texas centers. At present 44 infants have been enrolled including 11 from UT-Southwestern.

The UT-Southwestern site coordinated an observational study to determine whether a triad of high risk postnatal markers (delivery room intubation $\pm$ intensive resuscitation, 5 min. Apgar $\leq$ 5, and pathologic acidemia) could identify near term and term infants within the first 6 hours of age who are at greatest risk for developing moderate to severe encephalopathy, seizures, and abnormal short term outcome (3). This study was conducted over 11 months among 9 level III NICU's within Texas and included centers in Dallas, Houston, Galveston, El Paso, Austin and San Antonio. Dr. J. Perlman organized the study and interfaced with a single PI for each NICU. The latter individual was responsible for identification, assessment and data collection for each high risk infant. A total of 45 infants were identified from an estimated 100,000 deliveries. The relationship between the triad of markers, seizures, Sarnat stages and neurologic assessment at discharge is being analyzed.

II. NEONATOLOGY STAFFING

A. Principal Investigator (PI):

The PI for the UT-Southwestern site is Abbot R. Laptook, M.D. Dr. Laptook completed his fellowship training in 1981 from Brown University under the direction of William Oh, M.D. and he is board certified in Neonatal - Perinatal Medicine (1981). After fellowship, Dr. Laptook joined the faculty of UT-Southwestern and has risen academically to the present rank of Professor of Pediatrics and Obstetrics and Gynecology. Dr. Laptook holds important administrative roles, chief among them are Medical Director of the Newborn Nursery at Parkland Hospital (approximate annual admissions of 13,000 infants) and coordinator of Pediatric Grand Rounds at Children's Medical Center of Dallas. Dr. Laptook is a practicing neonatologist with four months per year of clinical service in the NICU and 2 weeks of clinical service in the Newborn Nursery. Fifty-five percent of his time is protected for research. Present clinical research efforts include the use of an integrated electroencephalogram for the diagnosis of hypoxic-ischemic encephalopathy, the role of infection and inflammation in the pathogenesis of hypoxic-ischemic encephalopathy, and the effect of magnesium on the neurologic assessment of the term and preterm newborn.

Dr. Laptook's laboratory research efforts have focused on 3 areas of ischemic brain metabolism which have the potential to impact critically ill human newborns and contribute to the development of brain damage. A newborn swine model has been developed and characterized over the first month of life to study the following areas:

1. Role of substrate availability and brain acidosis: In adults hyperglycemia during brain ischemia is

important in the pathogenesis of brain damage due to the development of profound brain lactosis and acidosis(4). The precise mechanism by which brain lactosis and acidosis leads to damage remains unclear. Vannucci et al(5) suggested that in contrast to the adult, hyperglycemia may be beneficial for the newborn, and the associated brain lactosis may be markedly reduced in the newborn. Drs. Corbett and Laptook used a complete cerebral ischemia paradigm to demonstrate that between birth and 1 month (a period characterized by a 2.5 fold increase in cerebral metabolic rate[6]), newborns have the same potential as older animals to generate high concentrations of brain lactate, although the newborn will reach this level more slowly than the older animal(7). Thus, newborns have a reduced time of exposure to brain acidosis/lactosis. In spite of the associated brain acidosis and lactosis, hyperglycemia may provide an advantage for the newborn during brain ischemia. Dr. Laptook has demonstrated that brain ATP is preserved at higher concentrations for hyperglycemic compared to hypoglycemic animals across a range of reduced cerebral blood flow(8).

2. Magnesium as a Neuroprotective Agent: There is great interest in the role of magnesium as a neuroprotective therapy based upon the retrospective observations of Nelson and Grether(9) and as evidenced by the Maternal Fetal Medicine Network undertaking the Beneficial Effects of Antepartum Magnesium (BEAM) protocol. Neuroprotection associated with Mg has been attributed to excitatory neurotransmitter receptor blockade, and thus Mg must readily enter the brain interstitium to allow interaction between Mg and neural cell surface receptors. To characterize the entry of Mg into the brain extracellular fluid (ECF) of newborn swine, microdialysis probes were inserted into the superficial cerebral cortex for measurement of brain ECF [Mg] during normoxia(10). Intravenous infusion of $MgSO_4$ increased plasma [Mg] to 4-6mM and resulted in a 193±76% increase in brain ECF [Mg] above control (latter set at 100%, $p<.01$). Identical experiments conducted during hypoxia-ischemia resulted in higher plasma [Mg] but similar brain ECF [Mg] as noted for normoxia. The lower ECF [Mg]/plasma [Mg] for hypoxic-ischemic animals suggests that entry of Mg into the brain is limited relative to normoxia. Thus, systemically administered Mg readily enters the brain interstitium, strengthening the rationale for use of Mg as a neuroprotective strategy. In separate experiments P^{31} Magnetic Resonance Spectroscopy (MRS) was used to assess the effects of $MgSO_4$ compared to Na_2SO_4 on brain energy state before, during and after hypoxia-ischemia. At the completion of hypoxia-ischemia and for 30 minutes following, the reduction in nucleotide triphosphates and brain pH was greater in $MgSO_4$ treated animals compared to the corresponding values for Na_2SO_4 infused animals(11). The direction of effect of these results would not favor neuroprotection by Mg and possibly even predispose to adverse neurologic outcome compared to animals with a lower plasma and brain [Mg]. These results are in agreement with other reports of the effect of Mg *in vivo* using newborn animals(12,13).

3. Studies of brain hypothermia: A series of experiments have been performed to examine the neuroprotection associated with a short interval (1 hour) and limited reduction in brain temperature (2-3°C, modest hypothermia). The rationale for studying short intervals of temperature reduction was to minimize the potential for the development of well recognized adverse effects of cold stress. When modest hypothermia was employed during or immediately after brain ischemia, partial neuroprotection could be demonstrated using both clinical and histologic outcome measures(14,15). However, when this hypothermia regimen was delayed for 30min following ischemia, neurologic benefit could not be demonstrated(16) (see Appendix). The results are consistent with the accumulating data that long intervals (days rather than hours) of brain cooling are necessary to achieve neurologic benefit when implemented at an interval after a brain insult (17,18).

One of the potential mechanisms by which profound hypothermia (> 10°C reduction) provides neuroprotection is by reducing energy expenditure. To determine whether modest hypothermia is associated with a similar effect, interleaved P^{31} and H^1 MRS were used to determine the brain energy utilization rate *in vivo* as a function of brain temperature (over a range of 30-40°C) in newborn swine. The results indicate a linear positive correlation between brain temperature and energy utilization rate, and predicts that for a 1°C reduction in brain temperature there will be a 5.3% reduction in brain energy utilization rate(19). Thus, modest hypothermia with a 3°C reduction in brain temperature will be accompanied by a 16% decrease in brain energy utilization rate and help to preserve ATP concentration either during or following hypoxia-ischemia.

Drs. Corbett and Laptook have applied H^1 MRS technology to non-invasively measure brain temperature. This work is based upon the principal that as temperature increases, the fraction of hydrogen bonds of water decreases, and the magnetic resonance frequency of the proton resonance shifts up field, due to hydrogen bond breaking and distortion. The methyl protons of N-acetylaspartate (NAA) and of similar compounds may be used as an internal chemical shift reference for making brain temperature measurements. The signal of H^1 magnetic resonance spectra from NAA is a prominent feature in spectra obtained from the brain, and these protons do not form hydrogen bonds and therefore do not shift with changes in temperature. This method was initially developed in model solutions and subsequently validated in neonatal swine over a broad temperature range comparing direct brain temperature measurements with temperature generated from magnetic resonance measurements; results yielded an excellent linear agreement (slope = 1.00±.03, r^2=0.96) (20) (see Appendix). This method has been used to determine the brain temperature of adult humans and results demonstrated temperature gradients from the deep brain structures (thalamus) to the brain surface (frontal lobe) (21). Further application of this technology tested the hypothesis that localized head cooling would reduce brain temperature in 10 normal adult humans (22). Cooling the surface of the head to 15.8±3.5°C did not reduce the temperature of the superficial cortex (36.8±0.5°C) compared to measurements of the superficial cortex (37.0±0.6°C) obtained with a head surface temperature of 34.7±1.6°C.

B. Faculty Providing Care to High Risk Infants

Name	Institution for Fellowship Training	Fellowship Yr Completed - Type	Acad. Rank	Clinical Service (mon) #	Research Time (%)
Blair Cox, MD	UT-Southwestern	Neonatal-Perinatal 1991	Assist. Prof.		
William D. Engle MD	University of Pennsylvania	Neonatal - Perinatal 1980	Assoc. Prof.		
Jeffrey Perlman, MBChB	Washington University	Neonatal - Perinatal 1983 Neonatal Neurology Cerebral Blood Flow & Metabolism 1985	Prof.		
Charles R. Rosenfeld, MD	Albert Einstein College of Medicine	Pediat Pulmonology 1971 Neonatal-Perinatal 1973	Prof.		
Walid A. Salhab, MD	UT-Southwestern	Neonatal - Perinatal 1997	Assist. Prof.		
Pablo J. Sánchez, MD	Columbia University UT-Southwestern	Neonatal - Perinatal 1980 Pediatric Infectious Disease 1988	Assoc. Prof.		
Philip W. Shaul, MD	Brown University	Neonatal - Perinatal 1986	Prof.		
Myra Wyckoff, MD	UT-Southwestern	Neonatal - Perinatal 2000	Assist. Prof.		

All faculty listed above are board certified in Neonatal-Perinatal Medicine except for Dr. Wyckoff who is finishing her fellowship in June 2000 and joining the faculty as of July 1, 2000. Drs. Rosenfeld, Laptook and Perlman also have appointments in the Department of Obstetrics and Gynecology. All of the faculty are well trained, highly

experienced in the care of low birth weight infants and high risk term newborns, and are actively involved in perinatal research. Specific information regarding administrative roles, and current research endeavors for each faculty member is as follows:

Blair E. Cox, MD
Administrative Role: Medical Director, Neonatal Nurse Practitioners, Parkland Hospital
Basic Research: Role of angiotensin II smooth muscle receptors in maternal-fetal and newborn blood flow, growth and development

William D. Engle, MD
Administrative Role: Perinatal Outreach Director
Clinical Research: Non-invasive measurement of bilirubin
Duration of antibiotic use in term infants with pneumonia
Determinants of blood pressure in low birth weight infants

Jeffrey M. Perlman, MBChB
Administrative Role: Medical Director, NICU, Parkland Hospital
Clinical Research: Pathogenesis of IVH and PVL
Diagnosis and epidemiology of HIE
Determinants of neurologic outcome in preterm infants
Delivery room resuscitation

Charles R. Rosenfeld, MD
Administrative Role: Division Director, Neonatal-Perinatal Medicine, UT-Southwestern
Director of Nurseries, Parkland Hospital
Clinical Research: Diagnosis and treatment of neonatal sepsis
Blood pressure control after birth
Basic Research: Regulation of uteroplacental blood flow
Ontogeny of vascular and visceral smooth muscle development
Estrogen mediation of vasodilation

Walid A. Salhab, MD
Administrative Role: Neonatal database management/Annual Report
Clinical Research: Determinants of chronic lung disease in preterm infants
Treatment of meconium aspiration syndrome

Pablo J. Sánchez, MD
Administrative Role: None
Clinical Research: Congenital syphilis (diagnosis, natural history)
Role of infections in the development of chronic lung disease
Methods to reduce vancomycin usage in NICU
Elective intubation and surfactant for RDS

Philip W. Shaul, MD
Administrative Role: Director of Intern Recruitment, Department of Pediatrics, UT-Southwestern
Basic Research: Endothelial cell biology: signal transduction and mechanisms of production of vasodilators including gene expression, intracellular traffic of signal molecules and enzyme activation

Myra Wyckoff, MD
Administrative Role: None
Clinical Research: Delivery room resuscitation and stabilization.

C. Faculty Providing Care to Term and Near Term Newborns

Name	Institution For Pediatric Residency	Yr Residency Completed	Academic Rank	Clinical Service (mon)	Research Time (%)
Greg Jackson, MD	Baylor College of Medicine	1975	Assoc. Prof.	#	%
Dorothy Sendelbach, MD	UT-Southwestern	1985	Assist Prof.		
Kaili Stehel, MD	UT-Southwestern	2000	Assist Prof.		

Dr. Sendelbach's appointment is part time (%). The major current research interests of the Faculty working in the Newborn Nursery includes use of the white cell count for diagnosis of infection, early hospital discharge and non-invasive measurements of hyperbilirubinemia.

III. AVAILABLE POPULATION

Parkland Hospital is the sole county facility for Dallas County, Texas. It is the primary teaching hospital of the UT-Southwestern Medical Center and provides accessible prenatal care through a network of 9 Community Oriented Primary Care health centers with delivery of mothers at Parkland Hospital. High risk pregnancies are triaged at any time during the pregnancy to a Complications Clinic situated at Parkland Hospital. The delivery population served by the UT-Southwestern site is listed in the following Table:

DELIVERY POPULATION OF PARKLAND HOSPITAL

	1996	1997	1998	1999
Deliveries (n)	13,614	13,578	13,429	14,438
Received Prenatal Care (%)	94	92	94	94
Ethnicity				
Hispanic (%)	71	72	74	77
Black (%)	20	19	18	16
White (%)	6	6	5	5
Asian (%)	2	2	2	1
Other (%)	1	1	1	1
Maternal Age < 20 yr (%)	22	21	22	20

Our delivery population peaked at 15,203 deliveries in 1992. With the growth of managed care and other health care reforms, all health care consultants used by Parkland Hospital predicted a large fall in the delivery population, ranging from 30-50%, and leaving an estimated delivery rate of 8-11,000/year. This has not happened and the fall off has only been approximately 10%. Furthermore over the past 18 months there has been a definite increase in the delivery rate; based upon the first 5 months of 2000, the projected delivery rate will be 14,800 for the year. In anticipation of a falling delivery rate in the mid-1990's, the UT-Southwestern site established a perinatal outreach program using St. Paul Medical Center as the primary referral hospital and Parkland Hospital was used for subspecialty services not available at St. Paul. This program consisted of enhanced communication with referring physicians, faculty and nursing lectures given at community sites, and a yearly one-day conference held in Dallas regarding updates in newborn medicine. Since August of 1999, the Parkland NICU has been able to accept few transfers from referring hospitals due to a census in the NICU often 25% above average. Further increases in the delivery rate will make it difficult to accept transfers from other hospitals.

= Months Devoted to Project

% = Percentage of Effort

Parkland Hospital is considered one of the finest public institutions in the nation and continues to make great strides in providing health care to the indigent. The creation of the Community Oriented Primary Care Program was critical in moving care from the tertiary center to the community. A state approved Medicaid managed care program has been created using Parkland Hospital and the Community Oriented Primary Care Program (Parkland Health First) and was initiated in September 1999. Parkland has also created a health care program for Dallas County residents who do not qualify for Medicaid and do not have access to other health insurance plans (Parkland Health Plus). Translation services have been enhanced due to the progressive changes in the delivery population with a primarily Spanish speaking population. Case workers for selected high risk pregnancies (e.g. preterm multiple births) and a perinatal intervention program for mothers who used illicit drugs during pregnancy are in place. Parkland Health and Hospital System continues to be a model institution with innovative programs to meet the needs of the population served.

Characteristics of newborns admitted to the Neonatal Intensive Care Unit are listed in the following Table:

NEONATAL INTENSIVE CARE ADMISSIONS AT PARKLAND HOSPITAL

	1996	1997	1998	1999
Admissions (n)	1,163	1,074	1,168	1,081
Outborn (n)	46	27	43	26
Ethnicity:				
Hispanic (%)	58	58	61	64
Black (%)	30	30	27	25
White (%)	10	9	9	8
Other (%)	2	3	3	3
Female (%)	45	45	46	45
Male (%)	55	55	54	55
Cesarean Section Delivery (%)	37	42	42	42
Maternal Prenatal Care (%)	90	93	91	92
Maternal Age < 20 yr (%)	25	23	26	23

In spite of the changes in the overall delivery population through the 1990's, the number of admissions to the NICU has remained relatively constant. The demographics has changed with a larger proportion of Hispanic infants compared to the prior Network submission; for example, in 1994, admissions to the NICU were 32% Hispanic and 45% black. Approximately 80% of the infants in the NICU are on Medicaid (either traditional or managed care), < 5% are in managed care or private insurance, and the remainder are charity. Due to the large volume of deliveries at Parkland Hospital, an Observation Nursery is in place in the Newborn Nursery to care for term and near term infants whose acuity of illness does not qualify for the NICU. The most common symptoms for infants in the Observation Nursery are hypoglycemia and tachypnea with onset more than 4 hours after birth. The number of patients admitted to the Observation Nursery during 1997, 1998 and 1999 were 1124, 1058 and 1672, respectively.

IV. MATERNAL FETAL MEDICINE UNIT:

The Obstetrics service at Parkland Hospital has a 29-bed antepartum high risk pregnancy unit that has been in continuous operation since 1972. Selected cases from this service are discussed at a joint Perinatal-Neonatal conference each week. Women in labor or in need of observation are initially evaluated in a Triage Unit. Depending upon assessment of obstetric risk, these patients are then moved to either a high or low risk Labor and Delivery Suite both of which are adjacent to the NICU at Parkland Hospital. Each of the delivery suites handle approximately 50% of the delivery population. The Triage and both Labor and Delivery suites are either new or renovated since 1988. The high risk Labor and Delivery Suite has 10 labor rooms, 4 delivery rooms and 5 operating rooms. The low risk Labor and Delivery Suite has 10 LDRs (labor, delivery and recovery rooms) and 2 operating rooms. A large Obstetrical ultrasound unit directed by the Department of Obstetrics is adjacent to the Labor and Delivery Unit. The Obstetrical service also has a large perinatal data unit which has been operational since 1983. This unit is housed 2 floors above Labor and Delivery, has 1,600 square feet of office space, 10 work stations and 4 dedicated research nurses and one data entry personnel to collect and enter data on all mothers and babies delivered at Parkland Hospital. This data has been used in over 100 publications and has enhanced the quality and organization of perinatal health care.

The Maternal Fetal Medicine Unit and Faculty are under the direction of Kenneth Leveno, M.D. who is Chief of Obstetrics at Parkland Hospital. There are 12 Maternal Fetal Medicine Faculty at Parkland Hospital, six are board certified and six are board eligible. The Maternal Fetal Medicine Faculty staff the high risk Obstetrics Complication clinic, the high risk antepartum in-patient service, and directly supervise all high risk pregnancies in the Labor and Delivery suites. The Maternal Fetal Medicine faculty are responsible for prenatal diagnosis and genetics, and Dr. Ron Ramus serves as the Medical Director. Dr. Ron Ramus also serves as the Co-Director of Ultrasonography along with Dr. Diane Twickler from the Department of Radiology. Dr. Leveno directs the perinatal data base and is the Principal Investigator for the UT-Southwestern site in the Cooperative Multicenter Maternal Fetal Medicine Units Network. He has been the PI or co-investigator for multiple randomized clinical trials conducted at Parkland Hospital. Over the past five years he has published extensively on delivery management of the Obstetric patient. Examples of recent work includes an evaluation of combined spinal-epidural analgesia compared to intravenous meperidine in 1,223 women (Anesthesiology 89:1336, 1998), effect of walking on labor and delivery in 1,067 women (NEJM 339:76, 1998), comparison of magnesium and phenytoin for the prevention of preeclampsia in 2,138 women (NEJM, 333:201, 1995), and a comparison of general and regional anesthesia for cesarean delivery in 80 pregnancies complicated by severe preeclampsia (Obstetrics and Gynecology, 86:193, 1995). Other active areas of clinical research ongoing at Parkland Hospital include preterm birth, diabetes, sexually transmitted diseases and childbirth related pelvic floor injury. Other notable and prominent Maternal Fetal Medicine Faculty includes Dr. Gary Cunningham who is Chairman of the Department of Obstetrics and Gynecology and Dr. George Wendel who has extensive experience in randomized trials for the prevention of transmission of HIV infection from the mother to the fetus. Dr. Wendel also collaborates closely with Dr. Pablo Sánchez in Neonatal-Perinatal Medicine regarding congenital syphilis and Group B streptococcal disease. A letter of support from Dr. Leveno is included.

V. FACILITIES AND CLINICAL CAPABILITIES

A. Facilities and Support Staff:

The Neonatal Intensive Care Unit (NICU) at Parkland Hospital has a 100 bed capacity. There are three levels of care within the NICU. The Intensive Care area has 24 beds distributed among three bays and an isolation room. Intensive care beds are equipped with state-of-the-art monitors which are interfaced with a single central monitor that allows real time monitoring, or storage and downloading for review of monitoring over the past 24 hours. A video EEG is permanently installed in the largest Intensive Care bay (10 beds). A negatively ventilated room is used for patients requiring isolation, critically ill infants requiring a quieter environment and/or additional room around the radiant warmer. The negatively ventilated room is also used as an operating area for ligation of PDAs within the NICU. One of the bays (6 beds) is used for patients with surgical conditions; clustering the surgical patients has enhanced the interactions between Surgical and NICU staff and promoted efficiency among the Surgeons in making rounds. The Intermediate Care Area has 44 beds distributed among four bays. Parkland Hospital is currently completing renovation of the Intermediate Care Area which includes provision of focused lighting for each infant, computerized controls to create a day/night cycle, installation of glass doors at the front of each patient bay, and use of sound reducing ceiling tiles to decrease noise levels. In addition, one bay has been converted into a Developmental Center designed for the care of eight chronically ill infants with a prolonged hospital stay. The Developmental Center will have more space around each bassinet/isolette to enhance maternal-infant bonding. The area is designed as eight individual modules with focused lighting, individualized bedside music, and state-of-the-art equipment to provide tactile and visual stimulation. The Continuing Care area has 32 beds, is housed separately from the Intensive and Intermediate Care areas, and serves as a transition nursery between the hospital and home. An overnight room for parents to room-in with their baby prior to discharge is in this area along with a four bed negatively ventilated isolation room.

The primary mechanism to maintain adequate nursing staff is achieved by conducting twice yearly nursing residences. The residency consists of a 13-week rigorous educational and clinical training course that all new nursing graduates, experienced nurses without NICU experience, and nurses with NICU experience outside of Parkland Hospital must participate in and pass a certifying exam. The residency is under the direction of a single dedicated nurse educator. A second nurse educator functions to keep all nurses within the Nursery service (NICU and Newborn Nursery) abreast of new developments and changes in policy. All high risk deliveries are attended by a Resuscitation team consisting of a nurse, respiratory therapist, senior pediatric resident and a fellow (the latter individual depends upon the specific case). Nurses on the Resuscitation team are part of a small cohort of nurses with enhanced delivery room skills. The NICU is staffed each month by 2 Attending Neonatologists, 1-2 Fellows, and 6 Pediatric Housestaff. Neonatal Nurse Practitioners supplement house officer coverage of the NICU, and Pediatric Nurse Practitioners care for infants in the

Continuing Care area to enhance maternal teaching and promote an effective transition to home.

Radiology services includes a dedicated room within the NICU to develop x-rays, view, read and store on site. A staff Radiologist reads films daily. Sonography is available with a dedicated color flow, pulse Doppler machine housed in the NICU. All CT and MRI procedures are performed at Children's Medical Center (adjoining Parkland Hospital) and the films are computerized and available for viewing at a terminal in the NICU Radiology room. A satellite Pharmacy is located within the NICU and operates from 7 a.m. to 11 p.m. The pharmacy is staffed by a Pharmacist and 1-2 technicians. There has been excellent interactions between the Pharmacy and NICU staff; pharmacy personnel actively participate on rounds and make recommendations regarding drug dosing regimens. A computerized program has been developed by Pharmacy and NICU personnel to avoid errors in ordering specific, frequently used medications. All medications for studies are handled through an Institutional Drug Service with 24-hour coverage. A Nutritional Support team includes a clinical dietician, a gastroenterologist and a pharmacist. The team provides weekly monitoring of high risk patients, is available for daily consultation, and assists patient providers with optimizing parenteral nutrition. The NICU is well supported by Respiratory Therapy with three therapists each shift and a blood gas machine within the NICU. Echocardiography is available within the NICU through the Cardiology service at Children's Medical Center. The central laboratory provides personnel for specimen collection at 0400 and 1600 hours. The NICU is equipped with a waiting area, conference room and office space for research personnel.

Children's Medical Center is physically adjoined to Parkland Hospital and provides state-of-the-art facilities for Radiology (MRI, CT Scan, contrast studies, fluoroscopy), Nuclear Medicine, and Interventional Cardiology (catheterization). All surgical procedures other than PDA ligation and placement of central venous catheters are performed in the operating suites at Children's Medical Center with recovery occurring in the Parkland NICU. ECMO services for neonates at Parkland are provided in the Pediatric Intensive Care Unit of Children's Medical Center.

B. Subspecialty Services:

The Department of Pediatrics at UT-Southwestern has 89 full time academic faculty providing the full spectrum of subspecialty clinical services. The main clinical divisions which serve the newborn population are noted below.

Pediatric Infectious Disease has 6 full time faculty available for consultation services. Their research interests include mechanisms of transmission and reliability of diagnostic tests for congenital syphilis and neonatal AIDS, the diagnosis and prevention of early onset Group B Strep infection, and the pathogenesis and treatment of meningitis. Drs. Nelson and McCracken are recognized leaders in their field and editors of the *Pediatric Infectious Disease Journal*. Dr. Pablo Sánchez, a member of the Neonatology division, is trained and board certified in Perinatal - Neonatal Medicine and Pediatric Infectious Disease.

Pediatric Cardiology offers diagnostic evaluation and consultation for patients at Parkland Hospital. The research interests of the 7 faculty include the molecular mechanisms of cardiac development, fetal echocardiography, pulmonary vascular reactivity, and the epidemiology of congenital heart disease.

Pediatric Gastroenterology offers evaluation and consultation for infants at Parkland Hospital. The staff is composed of 6 pediatric GI specialists with research interests that include lipid metabolism during development, gut-associated B-cell immunity, and developmental biology of the GI tract.

Pediatric Genetics and Metabolism consists of 2 MD-PhD's with expertise in clinical genetics and metabolic disorders. They provide consultation and multi-disciplinary follow-up care. Research interests include correlations between mapped genes and clinical phenotypes.

Pediatric Hematology-Oncology has 10 full time faculty. They offer clinical consultation in our NICU and have a variety of clinical and basic research interests including folic acid pharmacology, molecular biology of brain tumors, treatment of childhood leukemia, long term follow-up of cancer survivors, and mechanisms for inheritance of susceptibility to cancer. Our pediatric oncology program has been ranked as one of the nation's top cancer centers by the Pediatric Oncology Group, an international cooperative network of 110 medical centers founded to enhance research in the treatment of childhood cancers.

Pediatric Nephrology consists of 4 full time faculty with research interests in the ontogeny of renal tubular

ion transport, regulation of salt transport in the mature and immature kidney. X-linked hypophosphatemia, and metabolic bone disease in patients with spina bifida.

Pediatric Neurology includes 5 full time faculty. Their research interests include the diagnosis and treatment of neonatal seizures and the use of magnetic resonance imaging to characterize brain injury.

Pediatric Endocrinology has 4 full time faculty. Research interests include the molecular biology of adrenal steroid metabolism and thyroid disease in the newborn.

Pediatric Radiology includes 6 full time faculty and Pediatric Pathology has 4 full time faculty.

Pediatric Surgery includes 5 full time faculty. Other specialized services are the divisions of Pediatric Intensive Care, General Pediatrics, Pediatric Emergency Medicine Division, Pediatric Rheumatology, the Child Abuse Program and the Cystic Fibrosis Program.

C. NICU Follow-up Program:

The follow-up program for high risk infants from the Parkland NICU is located in the Bright Building, a new out-patient facility of Children's Medical Center of Dallas. The program has been directed by Dr. Sue Broyles for 9 years. Dr. Broyles is a member of the Division of Neonatal-Perinatal Medicine at UT-Southwestern and an Assistant Professor of Pediatrics. Following residency at UT-Southwestern she practiced pediatrics until 1988 when she did a fellowship in neonatal-perinatal medicine at UT-Southwestern (completed 1991) and focused on neonatal follow-up and epidemiology. Dr. Broyles at present works part time and additional medical staff coverage includes Dr. Roy Heyne, a pediatrician who has volunteered one half day a week in the clinic for 15 years, and Dr. Patti Hicks, a pediatrician in the Ambulatory Division who has a strong interest in developmental problems following prematurity. Due to the patient load and the results of the primary care trial (see below) the Department of Pediatrics at UT-Southwestern is actively recruiting a pediatrician or neonatologist to work in the follow-up program. The remainder of the staff is an extremely experienced group and the following list provides their years experience in the follow-up clinic at Children's Medical Center.

Jackie Hickman, R.N., Follow-up coordinator: 6 years experience
Elizabeth Heyne, Certified PA: 20 years experience
Sally Adams, Certified PNP: 12 years experience
Linda Madden, Certified PNP: 15 years experience
Kristin Dooley, M.S.-Developmental Specialist: 1 years experience

Ms. Hickman and Ms. Dooley are full time employees while Ms. Heyne, Ms. Adams and Ms. Madden each work % of full time. Social work, nutrition, physical therapy and occupational therapy services are available through Children's Medical Center.

Infants meeting any of the following criteria are eligible to be seen in the follow-up clinic: birth weight $\leq$ 1000gm, birth weight 1001 - 1500gm and ventilator therapy, ventilator therapy exceeding 1 week, grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, perinatal asphyxia and bowel resection. These criteria have previously been demonstrated to identify infants at highest risk for this population. In 1999 there were 2681 patient visits to the follow-up program. At present, there are 510 patients attending the follow-up program. Of this total, 148 are of a birth weight $\leq$ 1000gm, 10 are in the early iNO trial, and 3 are in the hypothermia trial. There are 122 infants in the BEAM study currently attending the follow-up clinic. Of the infants in the BEAM study, 73 infants do not meet any of the above criteria for attendance in the follow-up program but are being seen to meet the needs of the Maternal Fetal Medicine Network.

Avoiding loss to follow-up for high risk infants of indigent inner city families has been shown by Drs. Tyson and Lasky to be a challenge(23). Combining surveillance and evaluation for neurodevelopmental problems, management of complex chronic medical conditions, and routine pediatric care/immunizations greatly improves retention of patients in the follow-up program since health care is provided in a unified manner and in one physical location. Furthermore, Drs. Broyles and Tyson demonstrated in a randomized controlled trial conducted between 1988 and 1996 that access to comprehensive follow-up care reduced life threatening illnesses (manuscript under review, see Appendix). In this trial,

783 very low birth weight infants born at Parkland Hospital were randomized to either routine follow-up care (management of chronic illness, well pediatric care and use of community/tertiary care facilities for acute illness) or comprehensive follow-up care (routine follow-up care with care for acute illness). Each patient in the latter group was assigned to a PNP or PA from the follow-up program who was available by phone or pager at all hours to address acute problems. The primary care provider facilitated access to care for acute illness if deemed necessary, including transportation, contact with emergency room staff, and follow-up with the mother after care was provided to determine if further evaluation was necessary. The results demonstrated that comprehensive care reduced the total number of emergency room visits ($p<.01$), total admissions for intensive care ($p<.01$), total intensive care days ($p<.01$), and the percent of infants not attending the follow-up clinic at 1 year adjusted age (10.9 vs. 31.4%, $p<.001$).

The above findings have been incorporated into the Follow-up Program. Eligible infants in the NICU are identified by the Follow-up Coordinator within days after birth. The Follow-up Coordinator meets with the mother, preferably while she is still hospitalized, informs her about the Follow-up Program, and assigns a primary care provider for when the baby is discharged. The primary care provider (either Ms. Heyne, Ms. Adams or Ms. Madden) meets with the mother prior to discharge, gives instructions regarding communication by beeper or phone, and takes the mother to the Follow-up Clinic to familiarize her with the clinic. Infants discharged from the Continuing Care Nursery are seen in the Follow-up Clinic within 2 weeks of discharge and then at 2,4,6,8,12,18, and 24 months corrected age. Infants are seen in the Follow-up Clinic by their primary care provider for acute problems during clinic hours and are referred to the Children's Medical Center Emergency Room at other times. Dr. Broyles or one of the Neonatal Faculty serve as physician backup for the primary care providers when outside of clinic hours. When assessed at multiple intervals over the last two years compliance for any appointment in the Follow-up Program ranges between 60-70%, and compliance for new appointments ranges between 75-80%. The Follow-up Coordinator has been critical in tracking down mothers with missed appointments, getting them into the Follow-up Clinic and attaining a 90% follow-up rate for Network patients. The primary funding source for most patients in the Follow-up Clinic is Medicaid (either traditional or managed care). The majority of funding for staff personnel of the Follow-up Program is from Children's Medical Center with contributions from Parkland Hospital, the Department of Pediatrics at UT-Southwestern, and United Way.

Other investigations recently completed or ongoing within the Follow-up Program include the neurodevelopmental assessment of congenital infections (syphilis, cytomegalovirus and herpes), term infants with thalamic echos, and preterm infants with ventriculomegaly. Additional studies include an evaluation of Synergis to prevent RSV in preterm infants, a pregnancy prevention program for teen mothers with preterm infants (partially sponsored by the March of Dimes) and the effect of long chain polyunsaturated fatty acids in preterm formulas on growth and neuro-developmental assessment (Mead-Johnson).

D. Special Research Strengths:

The close collaboration of clinical and basic sciences in addressing major causes of morbidity and mortality is a major strength of the UT-Southwestern campus. Major areas of research on the campus have included control of hypercholesterolemia, mechanisms and treatment of cardiovascular disease and metabolic bone disease, molecular and genetic mechanisms of oncogenesis, as well as the pathophysiology and management of preterm labor and pregnancy-induced hypertension. The existence of interdisciplinary centers has fostered these research endeavors. Those of relevance for this proposal include the Cecil and Ida Green Center for Reproductive Biology, the Human Nutrition Center, and the McDermott Center for Growth and Human Development. These centers are supported by combinations of federal funds and private foundation and community support. Within the past year a Masters of Public Health Program has been established on this campus as a result of a partnership between UT-Southwestern and the Houston School of Public Health. Faculty in this Dallas-based program have a strong interest in maternal and child health.

VI. PERINATAL DATA SYSTEM:

Our Neonatology Division has developed and supported an extensive computerized clinical database since 1977. The current version of the database has been in use in the Parkland NICU since 1987 and was upgraded in 1999 to a Y2K compatible format. All infants admitted to the NICU and all neonatal deaths are included. We maintain one research nurse position to review charts and enter data into the database. The nurse has established written guidelines

and definitions for data entry. Drs. Salhab, Perlman, and Rosenfeld supervise and manage this endeavor. Our database includes over 300 data items, categorized as follows: Demographic/admission (25 items), Maternal (22 items), Pulmonary (36 items), Infections (11 items), Cardiac (16 items), Gastrointestinal (11 items), Neurologic (40 items), Hematologic (6 items), Ophthalmologic (6 items), Anomalies (9 items), Length of stay (75 items), Discharge/Follow-up (15 items), Miscellaneous (23 items), and Death (18 items). The database program includes on-line error checks as well as an error-checking program to identify incorrect, implausible, or missing data items. The program also includes a system for generating detailed annual reports for our neonatal unit. To indicate the timeliness and comprehensiveness of our data collection and analysis, the Appendix includes portions of the 1998 Parkland annual report. These provide the percent survival within a BW-GA age grid for the past 5 years at Parkland. We also include the Table of Contents for these reports which include data such as hospital occupancy data, survival data by BW and GA, disease-specific mortality and morbidity, duration of mechanical ventilation and hospital stay for survivors in different BW categories. The Department of Obstetrics and Gynecology maintains a computerized database including clinical data for all women who deliver at Parkland. The NICU Follow-up Program also maintains a clinical database with over 250 data items. The data from these databases can be exported into other formats so that customized data queries can be performed for descriptive research studies and for planning clinical trials. These databases can be easily linked to associate maternal data with neonatal and postneonatal outcome data. Our database has been used in planning and preparation of grants for numerous clinical studies within our division and a variety of published studies. Some recent examples include an analysis of the dose dependent effects of antenatal steroids on the outcome of VLBW infants (Salhab et al, Pediatr Res 45:318A, 1999), pattern of survival and resource utilization for VLBW infants between 1977 and 1995 (Kaiser et al, Pediatr Res 43:218A, 1998), relationship between delivery room events and oxygen requirement at 28 days of age for VLBW infants (Salhab et al, Pediatr Res 43:193A, 1998), analysis of predictors for survival of infants with congenital diaphragmatic hernia (Kaiser et al, J Pediatr Surg 34:1196, 1999), and the maturational dependence of the responsiveness of the patent ductus arteriosus to indocin (submitted as part of an RO-1, C.R. Rosenfeld, June 30, 2000).

While the Network maintains its own generic database, our division's database is of value to the Network for three reasons: 1) The experience of maintaining and using this database provide the PI and Alternate with knowledge of which data items will be feasible to accurately collect and which items will be most useful for clinical and research purposes, 2) It can be used to verify the accuracy of the Network data (collected independently by different research nurses than those responsible for our division's database), and 3) Our database can be used in planning Network studies when information is needed regarding data items or infants not included in the Network database. We have used our division's database as a supplement to the Network generic database to accurately estimate our planned recruitment for the current hypothermia trial and for the previously planned trial of tin-mesoporphyrin, and to verify the accuracy of our screening for inhaled nitric oxide use in the preterm infant.

VII. RESEARCH NURSING STAFF:

The Network Research Nurse Coordinator for the UT-Southwestern site is Ms. Susie Madison, R.N. She has been the Network Coordinator for the past 6 years and is well versed with the functioning of the Network. She has excellent working relationships with the staff of the Parkland NICU which has been fostered by 10 years of neonatal nursing experience at a level III NICU in Dallas. Through the Network studies, Ms. Madison has gained experience working with the Respiratory Therapy Department and the Investigational Drug Service at Parkland Hospital. Ms. Madison has also created a close interdigitated relationship with the staff of the Follow-up Clinic to insure that all Network patients are routed appropriately to the Follow-up Clinic at Children's Medical Center. Ms. Clara Alder, R.N. has recently been hired and works part time (0.5 FTE) in the Network. This is Ms. Alder's first experience functioning as a Research Nurse and she has an outstanding background of 16 years in neonatal nursing at a level III hospital to build upon. She has served as both a staff nurse and as a charge nurse with managerial skills.

VIII. PROTOCOL CONCEPT:

Title: Use of High Dose Phenobarbital For Neuroprotection Following Perinatal Hypoxia-Ischemia

Background: Hypoxic-ischemic injury in the near term and term newborn leading to the development of encephalopathy continues to be a difficult and challenging issue for the neonatologist. For the purpose of this discussion hypoxia-ischemia is equated with asphyxia since clinically important asphyxial episodes have some component of an alteration in perfusion pressure. Over the last 30 years there has been a shift in the focus of studies (both clinical and laboratory) concerning hypoxic-ischemic injury; over the first half of this period the emphasis of studies was to define

the entity of asphyxia and understand its relationship to outcome, and over the more recent 15 years there has been a greater focus on understanding the pathogenesis of tissue injury and earmarking specific brain oriented therapies.

The pathogenesis of brain injury and associated childhood neurodevelopmental deficits following perinatal hypoxia-ischemia is exceedingly complex and there are still large gaps in our knowledge base. A newborn animal model of hypoxia-ischemia has used P^{31}-MRS to demonstrate that there are two phases involved in the development of brain damage(24). There is an initial phase of primary energy failure (depletion of high energy phosphorylated metabolites and tissue acidosis) which resolves with resolution of the hypoxic-ischemic event and initiation of supportive intensive care. A subsequent phase of secondary energy failure characterized by depletion of high energy phosphorylated metabolites but minimal tissue acidosis occurs at an interval following primary energy failure and is sometimes referred to as delayed energy failure. Term infants following asphyxia at birth have been studied with P^{31}-MRS and both primary and secondary energy failure has been documented(25). The interval of time separating primary and secondary energy failure is characterized by a relatively intact cerebral energy state, and suggested that therapeutic interventions initiated after hypoxia-ischemia may still be effective in attenuating the extent of tissue damage. The elegant studies of Gunn et al(17) using a brain ischemia model in fetal sheep have demonstrated the presence of a therapeutic window.

Primary energy failure is initiated by an hypoxic-ischemic event and is a consequence of reductions in blood flow and O_2 delivery that result in decreases in brain tissue ATP and intracellular acidosis. Energy failure triggers a cascade of events many of which are interdigitated and run in both series and parallel. The latter involve loss of ionic homeostasis, elevated extracellular excitatory neurotransmitters, defective osmoregulation, mobilization of iron, reduction in protein synthesis and an elevation of intracellular calcium concentration(26). Resolution of the hypoxia-ischemia breaks the chain of events, but specific processes are potentially initiated with primary energy failure or reperfusion which predominantly manifest during secondary energy failure (e.g. peroxidative membrane damage, calcium activation of lipases and proteases). The events involved in secondary energy failure are far less clear but probably involve apoptosis, inflammatory mediators, and a secondary increase of extracellular neurotransmitters which act as excitotoxins(27).

A more complete understanding of cellular events involved in hypoxia-ischemia induced brain injury has guided the evaluation of potential therapies. A recent review by Vannucci and Perlman(2) summarized the current pharmacologic and non-pharmacologic agents under investigation. Most of these agents are in the laboratory phase and are directed at specific processes in the cascade of events leading to damage, e.g. excitatory amino acid antagonists and O_2 free radical inhibitors and scavengers. Other pharmacologic agents of potential use cannot be as easily classified and barbiturates represent one example. A number of mechanisms for neuroprotection have been proposed for barbiturates and include a reduction in cerebral metabolic rate(28), decrease in catecholamine release(29), free radical inactivation(30), decrease in cellular and vascular edema(31), sedation(32), and reduction of intracranial pressure(33). In adult animals barbiturate therapy (most commonly short acting compounds, either pentobarbital or thiopental) decreased the extent of brain damage for both focal and global ischemia models, and was effective when given before or immediately after ischemia(34-37). In contrast, there are few animal studies examining barbiturates in the fetus and newborn. Studies most often cited use pentobarbital in a protective mode (before asphyxia) and demonstrated a longer time to last gasp (38,39), a slower fall in pH and increase in PCO_2 during asphyxia(38,39), and a reduction in the severity of histologically confirmed brain damage(39). There are no studies of barbiturates used for brain resuscitation in the newborn.

Based upon the encouraging results in adult animals, a randomized controlled trial of thiopental was performed in adult comatose survivors of cardiac arrest(40). The results demonstrated no neurologic benefit in an extremely high risk population (1 month survival, 35% in both groups), but hypotension occurred more frequently with thiopental (60 vs 30% for thiopental and control, respectively). There have been 3 randomized controlled trials of barbiturates in term infants following hypoxia-ischemia which include neurodevelopmental outcome. Goldberg et al used a continuous infusion of thiopental over the first 24 hours after birth and could not demonstrate neurologic benefit based upon developmental assessment at a minimum of 12 months of age(41). Strengths of the study included use of a rigorous definition of asphyxia, early treatment (average age of initiation of thiopental, 2.3 hours), and blinded long term evaluation. Weaknesses of the study included lack of blinding of NICU providers, sample size calculation based upon a short term outcome (change in intracranial pressure), and use of phenobarbital to treat seizures in more than 80% of infants in each group. Similar to findings in adult animal and human studies, thiopental lowered blood pressure and the thiopental group received more pressor support than the control group ($p < .005$). In contrast, Hall et al reported that 40mg/kg of phenobarbital given to term infants following asphyxia was associated with an improvement in neurologic

outcome at 3 years of age (p = .003) (42). Although this was a randomized trial using a rigorous definition of asphyxia, there are a number of important methodologic limitations including: absence of blinding among NICU providers and evaluators of outcome, sample size was evaluated based upon a short term outcome (seizures), exclusion of a high number of infants post-randomization, relatively late initiation of treatment (average age of 5.8 hours), and the management of seizures was not clearly described. Control infants received a mean of 27mg/kg of phenobarbital in the first 24 hours compared to 39 mg/kg for the experimental group. The third study appeared in abstract form and reported no benefit from high dose phenobarbital therapy (30 mg/kg followed by 15 mg/kg) initiated before 4 hrs of age and with developmental follow-up at 6 years of age(43).

Rationale: The available data to demonstrate neuroprotection associated with barbiturates is equivocal. In addition, there are concerns regarding the effect of barbiturates on brain growth and development; the latter though refers to long term use and should not be of concern when exposure is limited over days. However, there are a number of considerations which would still favor study of phenobarbital for term infants suffering asphyxia. First, the study of Goldberg et al(41) is complicated by the development of hypotension associated with thiopental. Given the critical importance of perfusion pressure in the post-asphyxial state, the development of hypotension may obscure any barbiturate associated benefit. Second, at a minimum the results of Hall et al(42) raise the possibility that phenobarbital may be efficacious when high doses are used. Third, phenobarbital administered in a dose of 40 mg/kg was safe and well tolerated. This is a drug that readily enters the brain, the pharmacokinetics are delineated in the newborn, drug levels can be measured and obtained in all hospital laboratories, and neonatologists are comfortable using it. In contrast, many of the newer brain specific pharmacologic treatments have never been used in human patients, have unknown or undesirable side effects, and either do not penetrate the blood brain barrier well or require exceedingly high doses to enter the brain. Based upon these considerations, an appropriately performed randomized controlled trial of high dose phenobarbital for term infants with asphyxia can be justified.

Hypothesis: High dose phenobarbital therapy administered to near term and term infants at risk for adverse outcome following acute perinatal hypoxia-ischemia will reduce the incidence of death and/or disability at 18 months of age.

Experimental Design:

1. Patient Population: Inclusion criteria will be identical to the ongoing hypothermia trial except for one modification. Thus this study will include infants $\geq$ 36 weeks gestation with a pH (cord or within the first hour) $\leq$ 7.0 or base deficit $\geq$ 16 mEq/L, or a history of an acute perinatal event and either a 10 minute Apgar $\leq$ 5 or continued need for ventilation. All infants must have 3 signs of encephalopathy within 6 hours of age. The modification is that one of the signs of encephalopathy must be an altered level of consciousness. An alteration of consciousness, either lethargy or stupor, are the most important distinguishing clinical features of Sarnat stages 2 and 3, respectively.

2. Study Design: This will be a multicenter, randomized, placebo controlled , double blinded study.

3. Intervention: After enrollment, patients will be randomized to either phenobarbital treatment or a placebo for control infants. The duration of the experimental intervention will be the first 72 hrs following birth. Randomization will be performed by the Institutional Drug Service to maintain study personnel, NICU providers and family blinded to treatment assignment. Phenobarbital will be diluted in normal saline and 40mg/kg will be infused intravenously over one hour in the experimental group. The control group will receive a comparable volume of normal saline which will be infused intravenously over one hour. Initiation of experimental drug or placebo should commence as soon as possible after birth and not beyond six hours of age. Twelve hours after the initial dose of phenobarbital, therapy will be continued with four additional doses of phenobarbital, each 1.5mg/kg, given at 12 hour intervals. This regimen should result in a total phenobarbital level of ~ 40μg/ml through the first 72 hours of age given the prolonged half life of phenobarbital and the existing literature on the pharmacokinetics(44). The rationale for maintaining this level of phenobarbital over 72 hours reflects the time course of cellular events involved in primary and secondary energy failure in animal models(17). Infants in the control group will receive comparable volumes of normal saline intravenously to mimic the phenobarbital treatment. A single blood sample for a phenobarbital level will be obtained at 12 $\pm$ 4 hours following the last dose of phenobarbital or normal saline. Results of the blood level will be routed to a central Network site to avoid unblinding site personnel.

4. Intensive Care Management: Patients within each group will undergo evaluation for evidence of multiorgan

system dysfunction. A cranial ultrasound will be needed within 48 hours of birth to exclude other causes of encephalopathy. Acquisition of electroencephalograms is not a requirement for the study but is recommended for all infants with a clinical suspicion of seizure activity. An MRI of the brain will be recommended prior to discharge.

The most difficult and challenging aspect of this protocol will be to achieve comparable treatment regimens of seizures in each group and avoid or minimize contamination of the control group with phenobarbital therapy. Although it is widely stated in multiple reviews of neonatal seizures that phenobarbital is the treatment of first choice(45,46), a randomized trial of 59 neonates with seizures assigned to either phenobarbital or phenytoin therapy demonstrated that these drugs were equally but incompletely effective as anti-convulsants(47). Complete control of seizures was achieved in only 59% of neonates, confirming that effective treatment of seizures secondary to hypoxia-ischemia is difficult irrespective of what anticonvulsant is used. In view of these considerations there are multiple reports evaluating other anti-convulsants in small cohorts of neonates(48-50). Initiation of anti-convulsant therapy will be at the discretion of the Attending Neonatologist or Neurologist and the clinical care team, and will be based upon clinical or electroencephalographic evidence of seizures. Choice of anti-convulsants will follow specific guidelines to minimize the use of phenobarbital in the control group. Following discontinuation of the experimental intervention at 72 hours of age, the choice of anti-convulsant therapy will be at the discretion of the Attending Physician.

During the first 72 hours following birth, the anti-convulsant of first choice is phenytoin (20 mg/kg loading dose IV). Blood levels of phenytoin should be checked 1-2 hours following the initial loading dose with a goal level of 20-25 μg/ml. Additional phenytoin should be given to achieve this level; once attained maintenance therapy with phenytoin is continued over the first 72 hours at a dose of 5 mg/kg/day IV. Guidelines for initiation of a second and third anti-convulsant will include any seizure with a duration longer than one minute, any seizure with associated cardiopulmonary compromise irrespective of duration (clinical cyanosis, SaO_2 < 80%, heart rate < 90 bpm), or short seizures with a specific frequency of occurrence. If an infant meets any of these criteria, lorazepam will be used as the anti-convulsant of second choice (0.05 mg/kg IV). A second dose (0.05 mg/kg IV) can be given after 4 hours if seizures are not adequately controlled. Lorazepam is a benzodiazepine with potent anti-convulsant activity and has been effective in small cohorts of neonates with seizures secondary to hypoxia-ischemia and refractory to phenobarbital and phenytoin(49,52). A recent review of neonatal seizures proposed benzodiazepine derivatives as drugs of second choice(51). Data is available on the pharmacokinetics of lorazepam (0.05 - 0.1 mg/kg/dose IV) in 10 critically ill neonates with seizures; volume of distribution (0.76±.37 L/kg) and clearance (0.23±.11 ml/min/kg) were reduced and the elimination half life (40±16 hr) was prolonged compared to older children and adults(53). No appreciable adverse effects of lorazepam have been noted in reported cohorts, but respiratory compromise is a risk. If seizures persist in spite of drug therapy with phenytoin and lorazepam, use of phenobarbital will be unavoidable.

5. Use of Phenobarbital and Safety Considerations: For infants that meet criteria for a third anti-convulsant, phenobarbital will be administered as a loading dose of 20 mg/kg IV. Higher loading doses are to be discouraged since phenobarbital may be effective at lower doses when two additional anti-convulsants are in use, and the clinical care team will be blinded to whether their patients have received phenobarbital as the experimental intervention. To avoid potential toxicity from excessive phenobarbital administration to the experimental group, a phenobarbital level will be required 1-2 hours following phenobarbital loading as the third anti-convulsant. Phenobarbital levels will be reported to the Pharmacist and therapy will continue blinded if levels are < 65 μg/ml. If seizures continue, additional phenobarbital in doses of 5 mg/kg can be given with follow-up phenobarbital levels routed to the Pharmacist. Once seizures are controlled, maintenance phenobarbital therapy (1.5 mg/kg/dose IV q 12 hours) will be initiated 12 hours following the last loading dose. If phenobarbital levels are ≥ 65 μg/ml, results will be provided to the Attending Physician to avoid additional phenobarbital therapy. Although there is the potential for cardiovascular instability with excessively high phenobarbital levels, in general minimal adverse effects have been noted(54). This regimen should minimize contamination of the control group with phenobarbital treatment but provide sufficient safety and adequate treatment for infants with seizures resistant to therapy.

6. Outcome Variables: The primary outcome is the combined end point of death or moderate to severe disability at 18 months of age. Disability will be determined using a composite of Bayley Scales of Infant Development, Gross Motor Function, sensory deficits and seizures. Secondary outcome variables will include the following: frequency of clinically detected seizures, number of anti-convulsants clinically indicated, duration of mechanical ventilation, frequency of hemodynamic instability after initial stabilization, need for blood pressure support, frequency of non-CNS organ system dysfunction, frequency of neurologic abnormalities at discharge, frequency of CNS abnormalities on MRI prior to discharge, and length of hospitalization.

7. Sample Size: The sample size estimate will use the same assumptions as the present hypothermia trial: a two tailed type 1 error of .05, power of 80%, 10% rate of loss to follow-up, an incidence of 50% of death or disability in the control group, and the ability to detect a reduction to 30% in the intervention group. This gives a sample size of 100 infants per group and a total sample size of 200 for the trial.

IX. INTENT TO PATICIPATE

We intend to fully participate in a cooperative manner with other centers participating in the Network, with the NICHD, and The Data Center in all aspects of Neonatal Research as outlined in the RFA.

X. DEPARTMENT AND INSTITUTIONAL COMMITMENTS

See letters from Drs. Ginsburg, Rosenfeld, Perlman, and Leveno, and from Mr. Metoyer RRT. The Department of Pediatrics and Parkland Hospital have an outstanding track record of commitment to clinical research. This has been demonstrated repeatedly since the inception of the UT-Southwestern site within the Network, and enthusiastic support continues with the ongoing approval of all current studies.

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THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Kenneth J. Leveno, M.D.

Department of Obstetrics
and Gynecology

June 20, 2000

Abbot Laptook, M.D.
Professor
Department of Pediatrics
UT Southwestern
5323 Harry Hines Blvd.
Dallas, Texas 75390-9032
Campus Mail 9082

Dear Abbot:

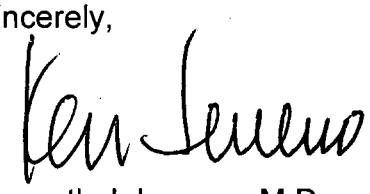
I write to pledge the full support of the Division of Maternal-Fetal Medicine and the Parkland Hospital Obstetrics Service for your application to continue as a center in the Cooperative Neonatal Units Network of the National Institute of Child Health and Human Development (NICHD). Let me emphasize that our maternal-fetal and neonatal collaboration is strengthened because UT Southwestern has also participated in the Maternal-Fetal Medicine Units Network of the NICHD. As you know, I serve as principal investigator for our maternal-fetal medicine unit and in this capacity, also offer you any assistance necessary in the research activities of your network. I have attached my biographical sketch in the event such data is useful to you. I also send you the following brief description of the obstetrics service at Parkland Hospital.

The Parkland Obstetrics Service is a coordinated, self-contained health care entity encompassing prenatal, intrapartum, and postpartum care. Obstetrical care is exclusively directed by the Department of Obstetrics and Gynecology of the University of Texas Southwestern Medical School. In 1999, 14,661 women delivered their infants at Parkland Hospital. We are proud that more than 96% of these women received prenatal care through our nine community clinics. I also mention that a computerized obstetrical database has been fully operational since 1983.

The members of the Division of Maternal-Fetal Medicine have extensive experience in clinical research protocols that include both single and multi-center observational and randomized trials. We have ongoing center-based research in hypertensive disorders, analgesia during labor, preterm birth, diabetes, sexually transmitted diseases, and prolonged pregnancy. We have also just begun a 5-year, NICHD funded study of childbirth related pelvic floor injury for which I serve as the principal investigator.

In summary, we offer you and your network the assistance of a large well-organized obstetrics service directed by a faculty committed to perinatal care, research, and education. We are most hopeful that you will be successful in re-competing to continue as a neonatal network center.

Sincerely,



Kenneth J. Leveno, M.D.
Gillette Professor of Obstetrics, and
Director of Maternal-Fetal Medicine,
Department of Obstetrics and Gynecology,
UT Southwestern
Chief of Obstetrics,
Parkland Health and Hospital System

KJL/bk

SOUTHWESTERN
THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Department of Pediatrics

July 3, 2000

Abbot Laptook, M.D.
Professor of Pediatrics

Dear Abbot,

I am extremely enthusiastic that you have chosen to reapply to NICHHD to maintain our status in the Cooperative Multicenter Neonatal Research Network. As you know, the Department of Pediatrics has strongly supported "the Network" since its inception at this University under of the direction of John Tyson. More recently, we have tried to provide you full support during the time that you have assumed responsibility for this enterprise.

The unbridled support from the Department of Pediatrics shall continue. Specifically, should the grant be refunded, we will continue to provide office, administrative and investigative space, direct access to and support from the Departments' business and grant personnel, any administrative support that is necessary and the availability of our information technology. Additionally, the University will continue to provide full support through our Grants Management, Grants Administration and Purchasing Departments.

I am extremely supportive and proud of the effort of the all of the participants on this grant. Certainly, participating in the Network has allowed us to make our enormous patient population and tremendous resources available to ask and answer important questions.

Good luck.

Sincerely,

Charles M. Ginsburg, M.D.
Professor and Chairman of Pediatrics
Marilyn R. Corrigan Distinguished Chair in Pediatric Research

Southwestern Medical School 5323 Harry Hines Blvd. / Dallas, Texas 75235-9063 / (214)648-3383 FAX (214)648-8617

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
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Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
and Professor of Obstetrics/Gynecology
Director, Division of Neonatal-Perinatal Medicine
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Lowe Foundation Professor
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June 28, 2000

Abbot Laptook, M.D.
Professor of Pediatrics
Division of Neonatal-Perinatal Medicine
University of Texas Southwestern Medical Center
at Dallas

RE: Neonatal Network

Dear Abbot:

It is with great pleasure that I provide you with this letter of support for our reapplication for funding by the NIH in order to remain a part of the Neonatal Network for Clinical Trials. As you know we have been a part of this network since its inception in 1986 and have been a very active and productive member of the clinical trials group, providing large numbers of patients in most of the studies that have been performed. One of the goals of the Division is to maintain this relationship with the NIH and the Neonatal Network for the foreseeable future. To achieve this goal, I am in full support of your application, and as in the past, will provide office space for your research nurses, as well as an area in which to maintain their computers in order to communicate with the database group and NIH.

In the past the fellows and faculty have been enthusiastic about this relationship with NIH and the Neonatal Group. We are committed to maintaining this role in the future. If you are in need of any further information, please do not hesitate in contacting me. I look forward to your leadership in this arena and to our staying a part of this important aspect of clinical investigation.

Very truly yours,

Charles R. Rosenfeld, M.D.
George L. MacGregor Professor of Pediatrics
And Professor of Obstetrics and Gynecology
Director, Division of Neonatal-Perinatal Medicine

THE UNIVERSITY OF TEXAS
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(214)648-2015

June 26, 2000

Abbot Laptook, M.D.
Professor, Department of Pediatrics
University of Texas Southwestern Medical
Center at Dallas

Dear Abbot:

It gives me great pleasure to provide you with a letter of support for your reapplication to the Multicenter Neonatal Network. Over the past decade the neonatal network has conducted numerous multicenter studies which have had an important impact on neonatal practice in this country. Our neonatal unit has contributed significantly to the continued overall success of the network. Since the departure of Dr. Tyson two years ago, the divisions contribution to network studies has continued at the same high level of competency and efficiency. This is a testament to your fine leadership qualities. Moreover, your intimate involvement in the planning and now successful implementation of the hypothermia study to prevent ongoing brain injury following intrapartum hypoxia ischemia has been equally impressive. Your outstanding fundamental knowledge of the regulation of cerebral blood flow and metabolism will be important to the network as it plans future studies related to the common neonatal neurologic disorders.

Once again as the medical Director of the neonatal Intensive Care Unit I want to enthusiastically extend my support and to facilitate in any way possible the studies of the neonatal network. I look forward to a continued fruitful working relationship in the years to come.

Sincerely,

Jeffrey Perlman, M.B.
Professor of Pediatrics
Medical Director, Neonatal Intensive Care Unit
Parkland Memorial Hospital

children's
MEDICAL CENTER OF DALLAS

June 20, 2000

Abbot R. Laptook, M.D.
Professor
Department of Pediatrics
UT Southwestern
5323 Harry Hines Blvd.
Dallas, Texas 75390-9063

Dear Dr. Laptook,

The staff of the Low Birth Weight Clinic is pleased to hear of your decision to reapply for the Neonatal Network Cooperative Research Grant. We wish to offer you our full support and to express our confidence in you as the new Principal Investigator. As you know, we have long supported the efforts of the NICHD Neonatal Network to conduct clinical trials of neonatal therapies and to assess infant outcomes well beyond the neonatal period. We feel strongly that our continued participation in this research program is essential.

In the last 10 years we have worked hard to address the health care needs of our low birth weight population. As a result we think our program is unique among neonatal follow-up programs. Our clinic was first established 20 years ago and has evolved over the years to provide comprehensive primary care in addition to the standard neurodevelopmental assessment offered by most neonatal follow-up programs. We have been able to demonstrate that in our population, such an approach not only results in better health outcomes for our infants, but also assures better follow-up rates and compliance with research protocols and developmental assessments. We are fortunate that both Children's Medical Center and Parkland Memorial Hospital have joined with UT Southwestern in support of our program and that we are able to work with other specialized primary care clinics in the new ARCH Center at Children's.

As you know, even the best of programs would not be successful without an experienced and dedicated staff. Jackie Hickman, R.N., our clinic coordinator is meticulous in her tracking and has worked in research follow-up programs since 1986. She interacts daily with both the Neonatal ICU staff, discharge staff and research nurses to assure accuracy of tracking information, communication of health care needs, and the personal interaction that is necessary to assure successful transition of our families from the neonatal ICU to the follow-up clinic. Our primary care providers are Liz Heyne, PA-C, Linda West-Madden, PNP and Sally Adams, PNP. They have worked in the Low Birth Weight Clinic

for an average of 15 years and are available by beeper to their clinic and study patients 24 hrs/day, 7 days/week. All are certified neurological examiners for the Network and are directly supervised by Dr. Roy Heyne, Dr. Patty Hicks, and myself. Cristin Dooly is our developmental specialist and is a certified Bayley assessor who has worked with our infants for 4 years.

The last year has been difficult and demanding, but we are successfully learning to navigate the new barriers imposed by Managed Care. Overall, we feel that our institution and our study population provide valuable and reliable information to the Network about the outcome of NICU graduates. We are optimistic about our chances of being selected and look forward to another 5 years of cooperative research with the NICHD Neonatal Network.

With sincere appreciation of your efforts,

Sue Broyles MD

R. Sue Broyles, M.D. (and the LBW Clinic Staff)
Professor of Pediatrics
UT Southwestern
Medical Director
LBW Clinic of Children's Medical Center

Parkland
Health & Hospital System

To: Abbot Laptook, MD
The University Of Texas
Southwestern Medical Center At Dallas
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
5323 Harry Hines Blvd.
Dallas, Texas 75235
Attn. Sandra Norris
(214) 648-8665

Parkland Memorial Hospital

From: Glenn Metoyer, RRT
Area Manager
Respiratory Care Department
Parkland Health & Hospital Systems
5201 Harry Hines Blvd.
Dallas, Texas 75235
(214) 590-8190

Community Oriented Primary Care

Parkland Community Health Plan Inc.

Parkland Foundation

I would like to convey my enthusiasm and support for your application to the NICHD Cooperative Multicenter Neonatal Research Network. It has been educational and rewarding for the Respiratory Care personnel to participate in the Early INO Trial over the past two years, and we will look forward to participating in future studies. The staff genuinely feels that the studies keep them on the cutting edge of neonatal care, and intensely heightens their professional job satisfaction. I assure you that the Respiratory Care Department at Parkland Health & Hospital Systems will provide you with the support that is needed to conduct the investigations of the Network.

Sincerely,

Glenn Metoyer

Glenn Metoyer, RRT

THE UNIVERSITY OF TEXAS
HOUSTON
HEALTH SCIENCE CENTER

Medical School
Jon E. Tyson, M.D., M.P.H.
Michelle Bain Distinguished Professor
of Medicine and Public Health

Director, Center for Population Health
and Evidence-Based Medicine

July 6, 2000

Abbot Laptook, MD
Professor of Pediatrics
UT Southwestern Medical Center at Dallas
Room E3-503
5323 Harry Hines Blvd.
Dallas, TX 75235

Dear Abbot:

It gives me great pleasure to write a letter of support for your application to the NICHD Neonatal Research Network. I am delighted that the past 2 years has been rewarding for you in directing UT-Southwestern as part of the expanded UT site. From the inception of the Network, the UT-Southwestern site has been a highly efficient Network center characterized by high enrollment rates among eligible patients, excellent compliance to protocols, and accurate and timely submission of data. The Low Birth Weight Clinic continues to have a strong track record with a follow-up rate close to 90%. During the past two years, you have established yourself as an extremely capable director for your site. I see no reason why the UT site should not continue as an outstanding Network center. Moreover, you would obviously make major contribution as a PI to the design and performance of future proposals, particularly those focusing on the prevention or treatment of brain injury. It is clear from your contributions to the Hypothermia Trial that the Network needs your special expertise in conducting highly important research to improve the neurological outcome of high-risk babies.

Sincerely,

Jon

Jon E. Tyson, MD, MPH
Professor of Pediatrics, Obstetrics,
Internal Medicine and Epidemiology

JET/ajr

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