

Fi <b>12142028</b>		Health and Human Services Public Health Service		OMB No. 0925-0001	
<b>Grant Application FEB 14 2008</b>		PI: <b>1 K23 HD'</b>		Council: 10/2008	
Do not exceed character length restrictions indicated		Dual:		Received: 02/14/2008	
1. TITLE OF PROJECT (Do not exceed 81 characters, including spaces and punctuation)		IRG: ZHD1 SRC(99)			
Career Development Award in Obstetric and Perinatal Clinical Research					
2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes (If "Yes," state number and title)					
Number: PA-05-143		Title: Mentored Patient-Oriented Research Career Development Award (K23)			
3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR <input type="checkbox"/> New Investigator <input checked="" type="checkbox"/> Yes					
3a. NAME (Last, first, middle)		3b. DEGREE(S)		3h. eRA Commons User Name	
ie		MD, MPH, PHD			
3c. POSITION TITLE		3d. MAILING ADDRESS (Street, city, state, zip code)			
Instructor/Fellow					
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT					
Obstetrics and Gynecology					
3f. MAJOR SUBDIVISION					
School of Medicine					
3g. TELEPHONE AND FAX (Area code, number and extension)					
TEL:		FAX:		E-MAIL ADDRESS:	
4. HUMAN SUBJECTS RESEARCH <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes		4b. Human Subjects Assurance No. FWA:		5. VERTEBRATE ANIMALS <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	
4a. Research Exempt <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		4c. Clinical Trial <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes		5a. If "Yes," IACUC Approval Date	
If "Yes," Exemption No.		4d. NIH-defined Phase III Clinical Trial <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes		5b. Animal welfare assurance no	
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: 12/01/08 Through: 11/30/13		7a. Direct Costs (\$) 120,363.		7b. Total Costs (\$) 129,944.	
		7c. Direct Costs (\$) 607,524.		7d. Total Costs (\$) 655,934.	
9. APPLICANT ORGANIZATION		10. TYPE OF ORGANIZATION			
Name		Public: <input type="checkbox"/> Federal <input checked="" type="checkbox"/> State <input type="checkbox"/> Local			
Address		Private: <input type="checkbox"/> Private Nonprofit			
		Forprofit: <input type="checkbox"/> General <input type="checkbox"/> Small Business			
		<input type="checkbox"/> Woman-owned <input type="checkbox"/> Socially and Economically Disadvantaged			
		11. ENTITY IDENTIFICATION NUMBER			
		DUNS NO.		Cong. District VII	
12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE		13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION			
Name		Name			
Title		Title			
Address		Address			
Telephone		Telephone		FAX	
E-Mail		E-Mail			
14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:		SIGNATURE OF OFFICIAL NAMED IN 13.		DATE	
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.		(In ink. "Per" signature not acceptable) 		2/11/08	

Principal Investigator/Program Director (Last, First, Middle):

**DESCRIPTION:** See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the mission of the agency). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

**In addition,** in two or three sentences, describe in plain, lay language the relevance of this research to public health. 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 purpose of this Mentored Patient-Oriented Research Career Development Award is to provide Dr. [redacted] MD, PhD (Epidemiology), with sufficient protected time as Assistant Professor in the Department of Obstetrics and Gynecology at the University of [redacted] : 1) develop advanced skills in the theoretical and practical aspects of the conduct of clinical research; 2) specifically, gain experience in the conduct of methodologically-rigorous clinical trials in obstetric and perinatal care; and 3) advance his skills in essential ancillary areas to clinical trial research such as cost-effectiveness analysis, metaanalysis, conduct of multi-center studies, grant-writing and the communication of research findings (including manuscript writing).

These skills will be acquired in a systematic fashion, as outlined in this research career award application. Dr. [redacted] will complete relevant focused courses and workshops (including formal courses at [redacted] School of Public Health) with a special emphasis on clinical trial design and implementation, cost-effectiveness analysis and metaanalysis. In addition to this formal didactic training, and with the guidance of highly qualified mentors and contributors, Dr. [redacted] will be responsible for all aspects of the implementation of 2 clinical trials: 1) a 3-arm clinical trial of higher doses of oxytocin versus current low-dose standard, in preventing obstetric hemorrhage, the leading cause of maternal mortality; 2) lead the development and implementation of a factorial trial of antibiotic prophylaxis strategies to prevent post-cesarean infection (also a major contributor to maternal morbidity and mortality), within the NICHD Maternal-Fetal Medicine Units Network (to which [redacted] belongs). Additionally, he will build on his prior work by conducting pilot studies exploring new avenues for preventing preterm birth.

These projects and others will provide the candidate with valuable practical experience and field expertise in the conduct of clinical trials and other obstetric and perinatal research. He will also gain increased expertise in several essential ancillary areas. The cumulative effect of this award will be to enable Dr. [redacted] to compete successfully for individual investigator NIH and other research funding, and ultimately to help advance the health and status of women and their infants in the US and elsewhere.

PERFORMANCE SITE(S) (organization, city, state)

1. University of [redacted]
2. NICHD Maternal-Fetal Medicine Units (FMFMU) Network

Principal Investigator/Program Director (Last, First, Middle):

KEY PERSONNEL. See instructions. Use continuation pages as needed to provide the required information in the format shown below. Start with Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
			PI
			Biostatistician

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
	& NICHD MFMU Network	Mentor
	& NICHD MFMU Network	Co-Mentor

Human Embryonic Stem Cells  No  Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/registry/index.asp>. Use continuation pages as needed.

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Use this substitute page for the Table of Contents of Research Career Development Awards. Type the name of the candidate at the top of each printed page and each continuation page.

**RESEARCH CAREER DEVELOPMENT AWARD  
TABLE OF CONTENTS (Substitute Page)**

Page Numbers

**Letters of Reference\*** (attach unopened references to the Face Page)

**Section I: Basic Administrative Data**

Face Page (Form Page 1) .....	1
Description, Performance Sites, Key Personnel, Other Significant Contributors, and Human Embryonic Stem Cells (Form Page 2) .....	2
Table of Contents (this CDA Substitute Form Page 3) .....	4
Budget for Entire Proposed Period of Support (Form Page 5) .....	5-7
Biographical Sketches (Candidate, Sponsor[s], * Key Personnel and Other Significant Contributors* —Biographical Sketch Format page) (Not to exceed four pages) .....	8-20
Other Support Pages (not for the candidate) .....	21-22
Resources (Resources Format page) .....	23-28

**Section II: Specialized Information**

**Introduction to Revised/Resubmission Application\*** (Not to exceed 3 pages) .....

**1. The Candidate**

A. Candidate's Background .....	29-30
B. Career Goals and Objectives: Scientific Biography .....	30-32
C. Career Development/Training Activities during Award Period .....	32-33
D. Training in the Responsible Conduct of Research .....	33-34

} (Items A-D included in 25 page limit) }

**2. Statements by Sponsor, Co-Sponsor(s),\* Consultant(s),\* and Contributor(s)\*** .....

34-49

**3. Environment and Institutional Commitment to Candidate**

A. Description of Institutional Environment .....	50-52
B. Institutional Commitment to Candidate's Research Career Development .....	52-54

**4. Research Plan (Two Projects - Page Numbers Separated by the "I")**

A. Specific Aims .....	55 / 60
B. Background and Significance .....	55-56 / 60-62
C. Preliminary Studies/Progress Report .....	56-57 / 62
D. Research Design and Methods .....	57-60 / 62-64

} (Items A-D included in 25 page limit) }

E. Human Subjects Research .....	64-65
Targeted/Planned Enrollment Table (for new and continuing clinical research studies) .....	65-67
F. Vertebrate Animals .....	68
G. Select Agent Research .....	68
H. Literature Cited .....	68-70
I. Consortium/Contractual Arrangements* .....	70
J. Resource Sharing .....	70

**Checklist** .....

71

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



Check if Appendix is included

Number of publications and manuscripts accepted for publication (not to exceed 5) \_\_\_\_\_

List of Key Items:

*Note: Font and margin requirements must conform to limits provided in the Specific Instructions.*

\*Include these items only when applicable.

**CITIZENSHIP**

- U.S. citizen or noncitizen national       Permanent resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award.)

**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: <i>Salary and fringe benefits. Applicant organization only</i>						
CONSULTANT COSTS						
EQUIPMENT						
SUPPLIES						
TRAVEL						
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT					
ALTERATIONS AND RENOVATIONS						
OTHER EXPENSES						
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
<b>SUBTOTAL DIRECT COSTS</b> (Sum = Item 8a, Face Page)		120,363	123,526	120,509	123,680	119,446
CONSORTIUM/ CONTRACTUAL COSTS	F&A					
<b>TOTAL DIRECT COSTS</b>		120,363	123,526	120,509	123,680	119,446
<b>TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD</b>						<b>607,524</b>

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

Please see the following pages for the budget justification.

## BUDGET JUSTIFICATION

### PERSONNEL

, MD, PhD, MPH, Principal Investigator (9.0-10.0 PM Calendar) is currently an Instructor/Fellow in Maternal-Fetal Medicine but will be an Assistant Professor when the award is made. He will, with guidance from his mentors, be directly responsible for the implementation of the projects as related to this award. He will participate in career development activities as outlined in the application involving travel to and attendance at scientific meetings, courses and workshops generally within the US. In addition, he will take two 3-credit hour courses at the School of Public Health during the award period. Books and software related to these courses on metaanalysis and cost-effectiveness analysis will be bought. In addition he will purchase books related to clinical trial methods. His training in cluster randomized trials will include 2 trips to Cameroon where planning for the trial is ongoing – only costs for air ticket are included in this budget (other related costs will be paid from other sources). He will devote 9-10 person months out of 12 calendar months per year to activities related to the projects proposed in this application. Please note that a portion of Dr. salary will be paid via institutional cost-sharing due to the amount of his salary and K23 award support limitations.

, Statistician (0.36 PM Calendar) is Associate Professor of Obstetrics and Gynecology and Director of the Data Management Division of the Center for Women's Reproductive Health (CWRH). Ms. s expertise is in perinatal epidemiology. She has participated in extensive research regarding the complex factors contributing to the etiology of low birth weight, intrauterine growth retardation, pregnancy complication, and prematurity. She was the principal investigator for the data management contract for the , a five year study comprising over 12000 visits conducted recently at our center. Additionally, she has been responsible for the data management and analysis of scores of research projects conducted in the department over 2 decades. She will direct the development and maintenance of the database for the oxytocin trial, data entry screens, data dictionary, and tracking systems. Additionally, she will assist in preparing the data collection forms and supervising the data collection, data transfer, and data verification of all study related forms and all individual project related data elements. She will be responsible for oversight of the development and preparation of the final data set, and the analysis of the data. She will be assisted in this effort by they are funded on alternated years). Ms will devote 3% effort in Year 1 (0.36 PM Calendar), and 5% effort in Year 3 (0.60 PM Calendar).

, RN, MPH (0.60 PM Calendar) has extensive experience working with SAS as well as other relational databases. She has already assisted on several analyses leading to publications or abstracts. Specifically, she provided data analysis support for Dr. preliminary studies on extended-spectrum antibiotic prophylaxis leading up to the factorial trial. She will assist Ms. and in creating and maintaining the project database for the proposed oxytocin trial as outlined above for Ms. In addition, she will assist in analyzing his pilot studies on antimicrobial-antibiotic interactions and provide the same services for other secondary projects the will conduct during the award period as outlined in his objectives. Her responsibilities will include assisting in the design of the file structures, data entry screens and the data dictionary, linkage of databases, data collection and analysis. Ms. will devote 5% effort (0.60 PM Calendar) in years 2, 4 and 5 of the award. Although her actual effort on this project will exceed the above, our department will pick up the remainder of her support.

**TBN, Research Nurse** (0.60 PM Calendar) will be a nurse practitioner in the Center for Women's Reproductive Health. The Research Nurse will be qualified to work on randomized trials as well as prospective observational studies. She will coordinate all aspects of the proposed studies, including supervision of support staff, assurance of adherence to patient care policies, develop methods of tracking and retaining the study participants, supply procurement, responding to data auditing queries, and assisting as needed with data collection activities. As a certified nurse practitioner, she will also perform physical assessments and collect biological specimens on study participants in the pilot studies that plans to design as a secondary

Principal Investigator/Program Director (Last, First, Middle):

objective for this award. Additionally, she will be responsible for all IRB reporting, regulations and documentations. The Research Nurse will devote time as follows: Year 1 & 4 - 5% (0.60 PM Calendar), Year 2 - 10% (1.20 PM Calendar), and Year 3 & 5 - 3% (0.36 PM Calendar). Expected time devoted in excess of the above will be part of our committed institutional support for Dr

#### Fringe Benefits

Fringe benefits associated with the salary request for these budgets have been calculated in accordance with our institute's Cost Accounting Standards Fringe Benefits Schedule. For faculty, a fringe benefit rate of 26.8% is utilized. For non-faculty staff, a fringe benefit rate of 30.0% is used.

#### Facilities and Administration (F & A) Costs

Facilities and Administration costs have been applied per the Program Announcement's (PA-05-143) guidelines at eight percent of the modified total direct costs.

No non-personnel budget items are considered "major" or unusual for the scope of work. Therefore, as instructed, we have provided no justification for the other budgetary categories.

Services provided by the pharmacy on the pitocin trial will be paid for by our department as part of our commitment to the candidate and are not included in this budget.

All costs related to the development and conduct of the factorial antibiotic prophylaxis trial including data management will be covered by the NICHD MFMU Network and are not included here (see related letters of support from Drs.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

<b>NAME</b>		<b>POSITION TITLE</b>	
eRA COMMONS USER NAME		INSTRUCTOR, OBSTETRICS AND GYNECOLOGY	
<b>EDUCATION/TRAINING</b> (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	MD	09/89-03/96	MEDICINE
UNIVERSITY OF	MPH	09/97-09/98	INTERNATIONAL HEALTH
UNIV. OF TEXAS	PHD	08/99-05/01	EPIDEMIOLOGY/ BIOSTAT*
COLLEGE OF MEDICINE, FT)	N/A	06/01-06/05	OB/GYN RESIDENCY
UNIV. OF ,	N/A	07/05-06/08	MFM FELLOWSHIP

\*Degree awarded 12/2004. FT = Fulltime

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE****Employment**

1996-1996 Medical Offi n, Fulltime  
 02/96-09/97 Medical Offi vince,  
 (Supervisor:  
 11/99-05/01 Research A ),  
 (Supervisor:  
 02/96-09/97 Teaching As  
 (Supervi:  
 06/01-06/05 Resident Ob sup:  
 , MI  
 07/05- date Instructor,  
 Fulltime

**Honors**

1989 Best candidate, Advanced Level General Certificate of Education Examination,  
 E  
 1989 C ; Government for medical studies.  
 1992-96 M  
 1997 B Shared Scholarship Award for  
 st  
 1997-98 M  
 2000 TI i, School of Public Health.  
 2004 W npetitive dissertation grant in women's  
 he  
 2004-05 Ac Medicine  
 2006 Recognition for excellence in medical education, Ob/Gyn department,

**Board Certification and Licensure**

1998- Education  
 2005- Licensed  
 2006- Diplomate.

**Professional Societies**

1996-  
 2000-

Principal Investigator/Program Director (Last, First, Middle):

2001-07 Jur  
2001- Me  
2004- Ass  
2007- Fel

**Publications**

• **Original research and theoretical treatises**

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• **Non-experimental articles**

Title: Motherhood  
200

: response to commentary.

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• Abstracts

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**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME		POSITION TITLE Associate Professor	
eRA COMMONS USER NAME			
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, *	BA, summa cum laude	1968	Mathematics
University, :		1977-1979	Fellowship, Math Stats
University of .		1990-1995	PhD program, Epidemiology

**A. PROFESSIONAL EXPERIENCE**

1987 – 1996	C	
1992 – 1998	C	
1993 – 2001	li	3Y.
	U	
1998 – 2003	F	
1996 – Present	C	n's
	F	
2001 –2007	A	at
	B	
2002 – Present	D	
2007 – Present	A:	at
	B	

**B. PUBLICATIONS**

C	ocial profile, maternal
C	
R	ategies for the
Cl	cigarette smoking on
R	n gestation to initiate
R	cesarean delivery for
Cl	

Principal Investigator/Program Director (Last, First, Middle):

Pe	patients with
Le	apy for fetal
An	of extended post-cesarean
Rc	Irrigation to
Je	dontal isease
Gc	mbilical cord stet Gynecol
Gc	Periodontal
Ar	ial microbial delivery. Am
Ar	antibiotics to
Ar	py to reduce
Vc	laxin, soluble
Gc	Birth Project: ( ),
Ar	ama Preterm mmation, and
Gr	ama Preterm us markers of
Kl	A pilot Transmitted
G	ama Preterm acental lesion etal Neonatal
Ti	linical trial of rse antibiotic-
Al	cillin-resistant
G	The his cultures in

Principal Investigator/Program Director (Last, First, Middle):

**C. Research Projects Ongoing or Completed During the Last 3 Years:**

**ONGOING:**

1 RO1 HD 02/01/02-01/31/07  
ial

A multi-center randomized clinical trial of cervical cerclage to prevent preterm birth prior to 35 weeks' gestational age.

**COMPLETED:**

1 RO1HD 4/01/03-3/31/06  
nt

The major goal of this project was to demonstrate if in utero infection or inflammation among preterm infants is associated with an increased risk of adverse neurodevelopmental outcomes.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME  Ph.D., M.D.	POSITION TITLE Professor
eRA COMMONS USER NAME	

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, ,	B.S.	1974	Chemistry
University of	Ph.D.	1980	Physiology
University of School of Medicine	M.D.	1984	Medicine

**A. Positions:**

1976-1980		University of Texas Health Science Center
1984-1988		
1988-1990		/ of
1990-1995		al
1990-Present		of
1995-Present		etal
1999-Present		ne,
2000-Present		
2000-Present		of Obstetrics and Gynecology,
2005-Present		University of

**Honors:**

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Meeting, San Francisco, CA, ;  
Society of Maternal-Fetal Mec

Obstetricians and Gynecologists  
Gynecology,

l for Outstanding Research published in *Obstetrics and*

**B. Selected Publications**

A	Maternal-Fetal bacterial
G	Preterm term birth. Am J
A	ester cervical
G	ctoferrin, other 2(3): MFMU Maternal- genital
G	n Prediction Gynecol
A G	Prediction rm birth Am J
A	ternal-Fetal Prevent
A	d spectrum stet Gynecol,
A	ve have learned
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G	) JC. h. Obstet
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A	antibiotics to

Principal Investigator/Program Director (Last, First, Middle):

G The preterm

G Preterm  
with Various Markers of

A Preterm  
markers of inflammation,

A sociation of asymptomatic  
ometritis in non-pregnant

G The Preterm  
rth of Males and Females

T Impact of  
6.

G Preterm  
salis, A Placental Lesion  
Growth. J Mat Fet Med

G The alabama preterm  
is cultures in very preterm

T Clinical trial of  
sible adverse antibiotic-

A Methicillin-Resistant  
et Gynecol (In Press).

A),  
n Utero Exposure to Acute  
n J Obstet Gynecol (In

Al  
idual Leukocytoclastic  
cript).

**C. Research Projects Ongoing or Completed (During the Last 3 years)**

**ONGOING**

R01AI 09/01/04 – 02/28/09  
(

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.

1 U01 HD: 03/01/06 – 01/31/11  
NICHD  
Center

The goal of this project is to accelerate the pace of premature birth research by focusing on global

Principal Investigator/Program Director (Last, First, Middle):

genomic and proteomic strategies and the dissemination of genomic and proteomic data to the scientific community.

U10 HD0.

04/01/06 – 03/31/11

NICHD

*Cooperative Agreement Application Multicenter Network of Maternal-Fetal Medicine Units*

To conduct large-scale clinical perinatal trials.

**COMPLETED**

1 RO1 HD0.

04/01/03 – 03/31/06

*ind . ent*

The major goal of this project was to determine if in utero exposure to bacterial infection or inflammation among preterm infants is associated with an increased risk of adverse neurodevelopmental outcomes.



Principal Investigator/Program Director (Last, First, Middle):

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 N

for in preterm pregnancy after a prior cesarean delivery

Principal Investigator/Program Director (Last, First, Middle):

38. E  
tc

**C. Research Support .**

**ACTIVE**

- 1. Co-Principal Investigator—  
1U01HD
- 2. Principal Investigator-- (

**COMPLETED**

- 1. Co-Investigator – Agency for Health Care Policy & Research. U.S. DHHS,  
Contract
- 2. Principal Investigator – n. NICHD
- 3. Principal Investigator – Midcare  
NICHD #1K24I
- 4. Co-Investigator –  
#HD-
- 5. Principal Investigator --  
Units  
NICHD #U10 HD?
- 6. Foundation Award to Establish an Electronic Perinatal Medical Record  
System in I  
2001 005.
- 7. Principal Investigator –  
University of s Foundation General Endowment Fund;  
March February ;

## OTHER SUPPORT

, PH.D., M.D.

### ACTIVE

5U01,  
NIH

09/15/2004 – 02/28/2009  
\$ Total Annual Direct

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.

Role: Investigator

5 U01 HD  
NICHD

03/01/2006 – 01/31/2011  
\$ Total Annual Direct  
*ter*

The goal of this project is to accelerate the pace of premature birth research by focusing on global genomic and proteomic strategies and the dissemination of genomic and proteomic data to the scientific community.

Role: Principal Investigator

### PENDING

PA-  
NICHD  
C:

12/01/2008 - 11/30/2013  
\$ Total Annual Direct  
*Birth*

In this application, we propose to use our existing research infrastructure, expertise, and experience in neurodevelopmental follow-up studies of children born preterm to accomplish several Specific Aims including: 1) characterize neonatal/infant morbidities, and long-term neurodevelopment among singleton children with late preterm birth, and 2) to compare these outcomes to those of a cohort of children delivered at term.

Role: Principal Investigator

Principal Investigator/Program Director:

**OTHER SUPPORT**

ACTIVE

1 U01HD 11/01/2005-10/31/2010  
NICHD \$ Annual Direct

The major goals of this project are to define the biochemistry of chloride and sodium transport in airway epithelial cells and clone the gene(s) involved in transport.

U10 HD 04/01/2006 – 03/31/2011  
NICHD \$ Annual Direct  
Cooperative Agreement Application Multicenter Network of Maternal-Fetal Medicine Units

To conduct large-scale clinical perinatal trials.

PENDING

None

Principal Investigator/Program Director (Last, First, Middle):

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## RESOURCES

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**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. If research involving Select Agent(s) will occur at any performance site(s), the biocontainment resources available at each site should be described. 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:

Clinical:

Please see pages 24 - 28 for a description of the Resources, as well as pages 50 - 52 for a description of the Institutional Environment

Animal:

Computer:

Office:

Other:

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**MAJOR EQUIPMENT:** List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

## FACILITIES AND OTHER RESOURCES

### Center for Women's Reproductive Health

In keeping with the goals of the University of \_\_\_\_\_, the Department of Obstetrics and Gynecology is committed to the pursuit of excellence in research, education and patient care activities. As a part of this commitment, the department pledged its administrative support to the Division of Maternal-Fetal Medicine to allocate necessary resources toward the establishment of a Perinatal Epidemiology Unit in 1982. The growth and success of this unit was widely recognized during its first 10 years of operation and the unit later became the \_\_\_\_\_ Center for Obstetric Research. Later, in recognition of the increasingly diverse research agenda, this center became designated as \_\_\_\_\_ Center for Research in Women's Health (CRWH) and ultimately the Center for Women's Reproductive Health (CWRH). Although the Center is involved in both service and instructional programs, its primary purpose is to develop and test new ideas, concepts, and mechanisms for improving health care to non-pregnant and pregnant women and reducing infant mortality and other poor pregnancy outcomes.

Once investigators have decided on the research question to be investigated, the mission of this research unit is to design and implement a research protocol which contains sound methodology, is ethically feasible, imposes no harm and minimal inconvenience to those participating as study volunteers, and has a sufficient number of patients enrolled to appropriately test the stated hypotheses with acceptable levels of statistical significance. Multidisciplinary collaboration, internal and external review, and interim analyses are examples of ways in which the Center assures that studies are conducted such that results obtained are scientifically valid. The ultimate purpose of the Center is to guarantee that all components of the research process, including design, data collection, data analyses, as well as dissemination of conclusions and interpretations to medical and scientific groups are appropriately and efficiently conducted. A major strength of the Center is the ability not only to conduct NIH-funded contracts and grants, but also to utilize databases created from these funded studies to answer other related research questions. This unit focuses its energy and attention upon new ideas and health care strategies which may prove to be valuable in improving various aspects of women's health or reducing poor pregnancy outcomes such as preterm birth, low birth weight, pregnancy-induced hypertension, and other medical complications of pregnancy. Over the past 15 years, many hundreds of abstracts and manuscripts have been generated from prospective projects and databases managed by the Center's staff.

Resources (space, staff, databases, etc.) in the center are made available to researchers through authorization by the Administrative Core. Research faculty are able to utilize the databases, the biologic samples, etc., and have access to the Center's patients. Our Center's senior faculty and administrators work with investigators to conceptualize a research project, to define realistic populations, recruitment goals, and to develop appropriate sample sizes. Center staff have been intimately involved in the development and preparation of the current proposal. The Center staff also performs financial management the Center grants and participates in the creation of budgets for its investigators' proposals. The CRWH offers a highly experienced team of researchers, study managers, and data collection personnel who can either be utilized directly on a new protocol, or who can serve as consultants for a specific grant. The staff includes research nurse clinicians who not only complete data collection activities, but also manage patient care if indicated by study design.

Organization: Dr. \_\_\_\_\_ is the Director of the Center for Women's Reproductive Health. The Center has three functional cores: 1) administration, 2) clinical operations, and 3) data management and analysis. Internally, a Steering Committee consisting of managers of the three cores and representation from selected protocol investigators meet weekly to address operational issues. The Steering Committee presents activity reports specific to research projects, prioritization of Center projects, and operational issues for Director and Board of Directors approval.

1) Administration. The Administrative Director for the Center is responsible for the administrative and financial duties of the unit. The current Director was the previous \_\_\_\_\_ and has been with the \_\_\_\_\_ its origin as the Perinatal Epidemiology Unit in 1982. The Nursing Director chairs a monthly formal two-hour session with the \_\_\_\_\_

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physician investigators and all research nurses and recruiters. The status of each Center protocol is reviewed in depth in regard to recruitment, quality of data, timeliness of reports, etc.

2.) Clinical Operations. Our clinical research operations unit is currently staffed by a research nurse manager, four Research Nurse Practitioners and five full time research nurse clinicians. This nursing team provides data collection for all patients enrolled in our studies. Our experience has shown that this nursing team establishes excellent rapport with the research project volunteers and patient compliance and the ability to complete outcome follow up is enhanced. The nurses are cross-trained in pairs or teams for all ongoing projects so that staff absences are covered and volunteer activities can continue in the event of a planned or unplanned absence. The outpatient clinical and research facility, staffed by this nursing team and supervised by the attending physicians in the Division of Maternal-Fetal Medicine, is open Monday through Friday 8:00 AM to 5:00 PM. Hospital studies are staffed 24 hours a day during the week and work on an "on call" basis during weekends and holidays to insure the appropriate and timely collection as well as initial processing of the research specimens.

Two full time patient recruitment and retention specialists (one of whom is fluent in the Spanish language) support the nursing team. One of these recruitment specialists was instrumental in achieving the required 90% follow up rate for children of mothers enrolled in the NICHD and NINDS sponsored study "Beneficial Effects of Antenatal Magnesium" that was conducted by the NICHD MFMU Network (see Preliminary Studies section [study number 4]). The follow-up rate at for this study at 24 months of age was 95%. The outpatient nursing team is also supported by two clinical nursing assistants, two data information coordinators, two office service specialists, and a laboratory technician. The Center for Women's Reproductive Health has a patient tracking system used exclusively for research participants that is separate and complimentary to the University-based appointment system.

3.) Data Management and Analysis Core. The Data Management and Analysis Division of the Center for Research in Women's Health is responsible for creating and maintaining the project data system, data quality control, patient tracking data, the creation of final analysis datasets, and assisting the principal investigators in the analysis of the data.

Patients are identified for recruitment into the study using our obstetric automated record system (OBAR). We have a single system for tracking all patients participating in studies in the CRWH. All personal data and contact information are retained in a single database that can be linked to individual project databases by the study number and one additional unique identifier. This system provides for a central location for all personal information to which access is limited to recruiters and key personnel.

Data forms will be developed for the study visit(s), labor and delivery course for chart abstraction, and neonatal course data chart abstraction. The data system will incorporate data entry screens that mirror the data forms. All entered items will have built-in range checks, and where appropriate, consistency checks with previously entered items. Skip patterns are built into the system to prevent entry of irrelevant or wrong data. Each data form will be identified by study number and one additional unique identifier but will contain no personal identifiers in order to ensure maximum confidentiality. Data are entered into the system for each visit within 2 working days of data collection. Missing data or incorrectly coded forms are identified and immediately returned to the nurse/data collector for correction. In addition, once a week all data forms are evaluated for consistency errors and missing fields by an extensive edit program. Edit lists are delivered to the data collection staff and corrections made where possible. Historically, our data entry operators have had a very low entry error rate.

In addition to the internal system edits, for each project we randomly sample a subset of forms, usually about 5%, and double enter them to determine error rate and to identify particular problems within the data system.

Hardware and Software. The Data Management and Analysis Division (DMAD) currently has 15 Pentium III, 8 Pentium IV, and 5 Pentium Dual Core computers each with a minimum of 256 MB, 133 Mhz SDRAM, and 5 GB 10 ms ATAPI hard drives. The DMAD also includes one laser Color printer, 10 HP LaserJet printers, as well as one HP ScanJet color scanner. All of our computers are networked with dual synchronized cluster servers operated by Windows 2003 Server Enterprise Edition. Each server has dual Xeon 3.06 GHz CPU with 2 GB memories and connected to SCSI drive array (RAID 10 Configuration) with 730 GB data storage

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currently. Windows XP and Windows 2000 are the primary operating systems installed on most of our personal computers.

Software development is performed in Microsoft Access 2000<sup>®</sup>, Access 2003<sup>®</sup>, SQL Server 2005<sup>®</sup>, Microsoft Visual Studio.Net 2005<sup>®</sup>, and Macromedia<sup>®</sup> Studio MX 2004. The programming languages and components used for software development are Visual Basic, Visual Basic.Net, Active Server Page.NET, Java, Script Languages, and ActiveX Data Object. Study protocols, manuals of operations, and data management manuals are written in Microsoft Word 2003<sup>®</sup> and published in Adobe Acrobat 8.0<sup>®</sup>. Tables and spreadsheets utilize Microsoft Excel 2003<sup>®</sup> and Microsoft PowerPoint 2003<sup>®</sup> is available for slide presentations.

Internet Information Server (IIS) 6.0 enabled with 128-bit SSL (Secure Socket Layer) is currently being used as the secure Web server for the DMAD. The Center maintains a secure Web site providing patients, residents, and employees access to relevant information about the department and the center. The IIS server is also used for secure data transfer for multi-center studies.

Data analyses are performed using SAS 9.1.3<sup>®</sup> and data conversions are done using DBMS Copy 7.0<sup>®</sup>. We also have access to other statistical software such as SPSS<sup>®</sup>, EpiStat, and Statistica<sup>®</sup> and N-query Advisor 7.0.

**Data Security.** To enhance security and protect the confidentiality of patient records stored on the computer, the system permits only authorized users to access the stored records. The activities that any individual user can undertake while within the data entry system is limited by the privileges associated with her identification code and enhanced password. The system is also password protected when data entry personnel step away for brief periods.

The patient records are strongly encrypted and authenticated by using Microsoft Access<sup>®</sup> Encryption method and SSL (Secure Socket Layer) with 128-bit encryption method while the database is transferred via HTTPS (HyperText Transfer Protocol Secure) for multi-center studies. The server certificate and private key of HTTPS server for data encryption and decryption are provided from VeriSign<sup>®</sup> and will be renewed annually.

Complete data backup tapes of the data are made daily. Complete system backup to a tape drive occurs weekly. A comprehensive strategy to ensure the safety of the data includes rotation of data tapes, storage of data at an off-site location, and the use of uninterruptible power supplies to provide blackout protection.

## **Facilities**

The research clinic is housed in 8115 square feet on the first floor of the CWRH. The clinic contains eighteen examination rooms. Five consultation/ interview offices are conveniently interspersed among the examination rooms for patient interview and consultation needs, and mini RN/MD workstations, complete with voice/data communications, are located in each bank of examination rooms. Also included on the first floor is a patient education classroom, a secured area to contain patient research records and a pharmacy room to securely house study medications. A spacious patient waiting area is equipped with a play area for children.

The third floor of the CWRH houses the research faculty and senior administrative staff, including the Director's suite and secretarial offices, and sixteen additional offices. Two conference rooms, complete with electronic AV equipment, are equipped for research presentations and site visits. A "Core Projects Area" is a working room for project development, a library of protocols and operations manuals from current as well as completed studies, planning of secondary and ancillary analyses from existing datasets, and all regulatory documentation for Center studies. Also available in the 8385 square feet of the third floor administrative area is a lounge and workstations for temporary staff and visitors.

A second floor containing 8,456 square feet is not complete (shelled in) at this time but a portion is under construction and is scheduled for completion in February 2008. This new construction will primarily provide additional clinical space but will free up additional space on the first floor that will be available for clinical research projects. Thus, a total of 16,500 square feet of new space dedicated solely to our Women's Health research agenda, in addition to the 17,000 square feet in our existing facility, is available. This facility will be the site for conduct of the long-term follow-up and neurodevelopmental testing proposed in the current application.

## **Laboratory**

**The Ob-Gyn Infectious Disease Research Laboratory.** This laboratory was established in 1990 and is under the direction of proposed mentor, Dr. \ The lab occupies approximately 3000 square feet

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on three different floors in the \_\_\_\_\_ Building, which is adjacent to \_\_\_\_\_ Hospital. The laboratory employs a full-time Research Assistant, \_\_\_\_\_, who is an ASCP certified medical technologist and who has special expertise and training in culture and identification techniques for aerobic and anaerobic bacteria. The laboratory also employs two full-time medical technologists (both ASCP certified) and a laboratory assistant. The laboratory is within the Department Obstetrics and Gynecology and operates under both an Alabama State license as a microbiology research laboratory and a Clinical Laboratory Improvement Act (CLIA) Certificate of Compliance.

In addition to its extensive experience in the culture and identification of both aerobic and anaerobic bacteria, the laboratory also has conducted or provided laboratory support for many research projects funded by both federal and industrial sources. It was the reference laboratory that performed and interpreted the approximately 6000 Gram stains of vaginal smears collected during the NICHD MFMU Network Multicenter Preterm Prediction Study. Also, the laboratory performed all of the ligase chain reaction assays for *C. trachomatis* infection in urine specimens collected in the \_\_\_\_\_ mydia Ancillary Study which was appended to its multicenter interventional trial of metronidazole to prevent preterm birth in women with bacterial vaginosis or *T. vaginalis* infection. The laboratory also served as the reference laboratory for a multi-center study performed at eight international sites under the direction of the International Clinical Epidemiology Network (INCLEN). As a part of this study, the laboratory performed Gram stains and evaluate over 3200 vaginal smears for the diagnosis of BV. Additionally, laboratory personnel have developed and published a self-teaching learning guide with complete instructions and color photographs of Gram stained vaginal smears. The learning guide is being used to assist INCLEN investigators to master the technique of Gram staining vaginal smears and interpreting them for BV diagnosis. The laboratory also has extensive experience in enzyme immunoassay techniques and has contributed to many publications using this technology. The laboratory recently added a Research Associate (MD/PHD) along with expansion of its molecular biology capabilities including conventional PCR and RT-PCR. Additionally, this laboratory now performs all routine prenatal lab tests, including Quad screens, for pregnant women receiving antenatal care in out system. This active research laboratory has provided or is currently providing the majority of the laboratory support for many current studies.

#### **Animal**

N/A

#### **Computer**

There are over 60 microcomputers in use throughout the CRWH and physicians offices. These computers are essentials in the storage, retrieval, and analysis of all data collected in our studies. (These computers are connected to the University network backbone thereby allowing access to the internet, data transmission over high speed ATM lines, libraries and Ovid Medline searches.) Our entire medical, prenatal, and labor and delivery record, including the newborn record, is computerized and placed in a SAS format. Therefore, we will have on every patient who has participated in our studies and the rest of the population as well, an extensive database from which to obtain pertinent medical data. Additionally, we have extensive experience in computerizing our biospecimen repositories allowing ease in tracking and retrieval of specimens as well as linkage to clinical databases. This experience and capability will be fully utilized in the conduct of the currently proposed research.

Our Department also has in place the Obstetrical Automated Record (OBAR), a highly significant resource for the Center for Research in Women's Health. The primary goal of OBAR is to provide up-to-date computer-based prenatal, labor and delivery, and postnatal data wherever obstetrical patients are seen in the County Department of Health and/or the \_\_\_\_\_ obstetric health care systems. The OBAR database contains nearly every detail of prenatal and perinatal data on our patients including over 1000 variable fields. In addition to the clinical information (and crucial to the current project) OBAR also contains valuable (and regularly updated) tracking information such as addresses and phone numbers of patients, family, and other contacts. Over the years, OBAR has been an extremely significant resource providing additional tracking of our participants who have subsequently become pregnant in the interim from the last birth to the initiation of follow-up studies. As a tracking resource, OBAR has also proved extremely valuable in identifying and locating women within our system for recruitment into clinical trials. As an excellent example, The OBAR system and our full-time recruiters were instrumental in achieving the high rates of successful follow-up accomplished in

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the two previous childhood neurodevelopmental longitudinal studies described in detail in the Preliminary Studies section of this proposal (study numbers 6 and 7). In many respects, from a tracking and recruitment point of view, these studies were very similar to the currently proposed study. Another example is the usefulness of this system in achieving the excellent follow-up to date (95%) in the NICHD and NINDS sponsored study "Beneficial Effects of Antenatal Magnesium" recently completed by the NICHD MFMU Network. We plan to utilize the OBAR system to full advantage in the currently proposed project. The OBAR system database will be linked to the women participating in this project.

#### **Office**

: , as well as the proposed mentors, has office space on one of five adjacent floors of the Building contiguous to the Hospital. The candidate and mentors also have adequate secretarial support. The CWRH also offers administrative and data management office space on the third floor. As mentioned above, the third floor of the new facility houses the research faculty and senior administrative staff of the Center for Research in Women's Health, including the Director's suite and secretarial offices, and sixteen additional offices.

Summary. Based on our prior success, we believe that the resources and environment available to the candidate is clearly adequate to accomplish the stated specific aims for this training grant.

## 1. THE CANDIDATE

### A. CANDIDATE'S BACKGROUND

Dr. [redacted] long-lasting interest in maternal and perinatal health care issues was kindled by both the experiences of overhearing his mother conduct deliveries at an early age and actually observing childbirth for the first time in medical school in [redacted]. The applicant's M.D. thesis research was a small randomized clinical trial (RCT) of sedative therapy in the management of threatened miscarriage. Also, while in medical school, he organized a preparatory course for the competitive entrance examination into the medical school, an early demonstration of his preference for academic activities. After graduation, he worked as a medical officer providing general medical and public health services in a developing setting and witnessed the magnitude of maternal and perinatal morbidity and mortality. Public health skills seemed vital for optimal practice in that setting.

Dr. [redacted] therefore pursued training in Public Health (M.P.H) in the [redacted] after securing full funding through a competitive [redacted] government scholarship. Recognizing the essential role of research for improving health outcomes in all settings, motivated him to further his training in research methodology (Ph.D in Epidemiology with minor in Biostatistics). During this time, he groomed his academic skills by also working part-time both as a research associate in reproductive epidemiology and as a teaching assistant for advanced epidemiology courses. These experiences launched him on an academic career path and yielded peer-reviewed publications, some as first author. He also pursued residency training in Obstetrics and Gynecology at College of Medicine in [redacted] from 20[redacted] serving as administrative chief resident. To satisfy concurrent requirements for a residency research project and his epidemiology dissertation, he successfully competed for a dissertation grant in women's health from the Woodrow Wilson Foundation, and conducted a population-based observational study to ascertain the prevalence and determinants of health workers' awareness and use of simple evidence-based reproductive interventions in a developing setting. This work led to two first-author peer-reviewed publications and formed the basis for a proposed cluster randomized intervention trial. Dr. [redacted] obtained a small planning grant from the NIH Framework Program for Global Health through the [redacted] (2006 to 2007) to begin planning that trial. He continues to work with local collaborators to plan this community-based trial and to obtain funding.

To acquire in-depth and cutting-edge knowledge and skills in obstetric and perinatal health, [redacted] will complete three years of sub-specialty training in Maternal-Fetal Medicine at the University of [redacted] at [redacted] this summer. His research activity during this time has been considerably productive and includes specific research projects, topical reviews and epidemiologic appraisals covering various obstetric and perinatal topics. These have led to several first-author peer-reviewed publications in collaboration with senior and junior scientists (as evident in his bio-sketch), ample evidence of the candidate's ability to interact and collaborate with other scientists. Two of those publications - discussed later in this application - address 1) the impact of extended-spectrum prophylactic antibiotics on post-cesarean infectious morbidity, and 2) antibiotic-microbial interactions and adverse birth outcomes in a randomized trial of interconceptional antibiotics. The latter manuscript was an "Editor's Choice" article in the American Journal of Obstetrics and Gynecology. Dr. [redacted]

[redacted] has also presented his research findings both orally and as posters at national meetings including that of the Society for Maternal Fetal Medicine (SMFM). Last year he gave an oral plenary presentation on the impact of antibiotics on the endometrial microbial flora in high risk women and this year gave another oral presentation on the impact of timing of elective cesareans on adverse neonatal outcomes. Dr. [redacted] academic activities have also extended to the mentorship of resident physicians and graduate students conducting research projects. He has served as reviewer for several scientific journals. All these activities demonstrate the candidate's firm commitment to academic endeavors and potential to develop into a productive clinical investigator.

The candidate's long term career goal is to help improve obstetric and perinatal health care globally, primarily through research but also through education of future scientists and the provision of clinical and public health services. His general research interest involves the application of appropriate epidemiological, biostatistical and clinical methods to improve obstetric and perinatal health. Specific areas of interest include obstetric hemorrhage, infections, hypertensive diseases of pregnancy, thromboembolism, cesarean delivery, preterm labor and birth defects - all directly related to the major causes of maternal and perinatal morbidity and mortality in the US and elsewhere. It is clear from the above description and a review of [redacted]'s biosketch

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that his prior training and activities strongly correlate with his long-term objectives and career plans, and indicate high potential to develop into an independent investigator.

Upon completion of his fellowship, I [redacted] will remain in the Department of Obstetrics and Gynecology at the University of [redacted] and, from July of 2008, assume a fulltime tenure track position as Assistant Professor within the Divisions of Maternal-Fetal Medicine and International Health. He is therefore applying for this mentored patient-oriented career development award to acquire advanced research training needed to expeditiously evolve into a productive, independent investigator in patient-oriented research. The specific objectives he plans to accomplish are outlined in the next section.

### **B. CAREER GOALS AND OBJECTIVES: Scientific Biography**

As outlined above, I [redacted] has already acquired some research training in maternal and perinatal health and has strong relevant clinical background. This patient-oriented research career development award will help provide him with significant protected time (from purely clinical work) and additional resources over 5 years to acquire advanced training and receive focused mentorship in conducting high impact obstetric and perinatal clinical research, thereby becoming competitive for NIH research project (R01) and other grant support. His 4 specific objectives and how they fit into his past and current research activities now follow:

- i. To obtain advanced training in the design and conduct of complex obstetric and perinatal clinical trials: This is the primary objective Dr [redacted] plans to accomplish with the award. Recognizing the importance of clinical trials for innovating and improving health care (e.g., translating the discoveries of biomedical science into clinical settings), Dr [redacted] plans to gain advanced didactic training and practical experience in the conduct of randomized trials. This objective will build significantly on his prior training on clinical trials as outlined above and in his bio-sketch. To accomplish this objective he will attend a selection of pertinent graduate courses, workshops, seminars and conferences, which are outlined in the section on "research activities" below. In addition to these didactic activities, and with the appropriate mentorship and support, he will spearhead the design and conduct of 2 RCTs, which are currently being planned within the Maternal-Fetal Medicine Division and the Center for Women's Reproductive Health of the department of Obstetrics and Gynecology at [redacted]

The first study supported by departmental funds is a 3-arm RCT of higher vs. standard doses of prophylactic oxytocin at vaginal birth to assess a dose-response impact in preventing uterine atony and obstetric hemorrhage. The institutional review board (IRB) of [redacted] has already approved this study (Appendix A). The second study is a 2x2 factorial RCT of two antibiotic prophylaxis strategies to prevent post-cesarean infection. The strategies involve antibiotic spectrum (extended-spectrum regimen i.e., cefazolin + Azithromycin vs. standard regimen i.e., cefazolin only) and timing of administration (before surgical incision vs. after cord clamping to avoid fetal exposure). Dr [redacted] presented this factorial trial concept for study within the NICHD's Maternal-Fetal Medicine Units (MFMU) network, to which [redacted] belongs, and it was approved on January 11<sup>th</sup> 2008 (see letters of support).

These 2 studies, which are detailed in the "Research Plan" section below, will be conducted under the mentorship of [redacted] D, MD (Vice Chair and Division Director for Maternal-Fetal Medicine) and [redacted] MD, MSPH (Director of the Center for Women's Reproductive Health and Principal Investigator for [redacted] site of [redacted]).

- ii. To design and conduct pilot studies exploring the potential role of antibiotic-microbial interactions in preterm birth and pregnancy loss: A recent study first-authored by [redacted] suggested a novel mechanism that might underlie the occurrence of pregnancy loss and preterm birth: antibiotic-genital tract microbial interactions [redacted]. The study, based on a prior clinical trial of interconceptional antibiotics among women at high risk for preterm birth work by conducted by Dr. [redacted] was published as an "Editor's Choice" paper. The findings indicated that in the presence of colonization of the upper genital tract by specific microbes, intake of antibiotics was associated with an increase in pregnancy loss and preterm birth. However in the absence of those microbes, antibiotics instead reduced the occurrence of preterm birth/pregnancy loss among high-risk women. Although these findings are hypothesis-generating, the plausibility of the hypothesis is reinforced by another related study also first-authored by the candidate, indicating that new colonization with the same microbes implicated in the interaction (gram-negative rods, particularly *Gardnerella vaginalis*) was actually prevented by the antibiotic regimen among women negative at baseline, while the resolution of existing colonization was enhanced [redacted]

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2 These consistent observations strongly suggest real biologic interaction between antibiotics and microbes. With the mentorship of Dr (senior author on both manuscripts) who will also make available the resources of his laboratory, one secondary objective of the applicant will be to conduct a comprehensive review and design pilot studies to further elucidate this issue. The candidate will seek to obtain small grants funding (R03 or other) to support these pilot studies. The pilot data generated during the award period could form the basis for an independent clinical research project with R01 or similar funding. Training in relevant laboratory techniques utilized in Dr laboratory, and the collection and handling of patient specimens from the pilot studies will provide introductory experience in translational research.

iii. To continue planning a cluster randomized intervention to improve maternal and perinatal health care in a developing setting: 's prior research documented in 2 peer-reviewed publications [

3] revealed poor awareness and use of evidence-based interventions that reduce maternal and perinatal morbidity and mortality among health workers in . Drawing from these findings, I secured an NIH-sponsored Framework Program for Global Health planning grant at and has been working with local collaborators (using a participatory approach that involves input from local reproductive health workers) to develop an intervention strategy aimed at improving the use of effective interventions. A cluster-randomized trial with individual reproductive health care facilities as the unit of randomization, (although the study unit will still be individual pregnant patients) is also being planned to evaluate the effectiveness of the program. Dr. (Co-Mentor) and Dr. who provided one of the candidate's reference letters) are involved with this initiative. recently first-authored a related commentary providing an overview of the safe motherhood initiative highlighting the need for more rigorous evaluation, particularly through cluster randomized trials where feasible, of policies proposed to reduce maternal mortality in developing countries prior to their widespread implementation, .

Therefore, a secondary objective of Dr during the award period will be to continue to develop these initiatives and further advance his experience in conducting cluster-randomized studies. Although this secondary objective involves a foreign site, the activities involved are absolutely consistent with Dr. primary objective for the award – to acquire skills in conducting complex trials. To complement the practical experience, Dr. didactic training program will include courses/workshops on the conduct of cluster-randomized trials.

iv. To acquire practical training and experience in other ancillary areas important for a productive independent clinical research career: [ ] plans to use the mentorship and training opportunities afforded him by the career development award to advance his abilities and knowledge in a) Communication of research data (manuscript preparation, oral presentations, tips for preparing slides), b) Grant-writing and obtaining extra-mural funding, c) Metaanalysis of clinical trials d) Cost-effectiveness analysis, and e) Structure and functioning of multi-center research collaborations.

To accomplish the above objective, the candidate will pursue both didactic training through select graduate courses, workshops or seminars on the different topical areas and hands-on experience by writing manuscripts and grant applications during the award period. A grant-writing workshop to train investigators to write high quality, competitive grant applications is offered at Dr. will also attend Faculty Development Courses that among other issues provide information on sources of research funding and training in writing grants. Some of these courses are offered by Faculty Development Office. Practical training will be acquired through ongoing grant-applications as appropriate including intramural grants, R03, and participation in obtaining institutional grants such as the Fogarty International Center training grants as well as funding from private sources. The candidate expects to successfully obtain R-01 or other equivalent funding as PI within a year of the end of the award period. The candidate plans to take two 3-credit hour graduate level courses: one on metaanalysis and the other on cost-effectiveness analysis. The courses selected will provide more advanced training in these 2 areas than the introduction the candidate received as part of his PhD program. The applicant plans to conduct an actual metaanalysis of all trials of extended-spectrum prophylaxis specifically focused on those which have used a 2<sup>nd</sup> antibiotic (Azithromycin, Gentamycin and Flagyl) that does not belong to the Beta-lactam class. This issue is closely related to the second trial proposed by Dr (see the background section) and no existing metaanalysis has addressed this question. The candidate also plans cost-effectiveness analysis projects to assess different oxytocin dosing regimens and strategies of antibiotic

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prophylaxis, topics closely related to the 2 projects proposed to attain the primary objective. All of the above will lead to manuscripts for peer-reviewed publication and presentation at various scientific meetings including the SMFM annual meeting. In addition, applicant will continue to carry out other pertinent research analyses based on the multiple departmental research and clinical databases and those of the MFMU Network. All these will create ample opportunities for acquiring experience in the diverse skill sets required for effective communication of research findings (manuscript-writing, preparing slide presentations, public speaking, dealing with the press). Informal feedback will be obtained through rehearsals at the weekly divisional research meeting (required for all oral abstracts), and presentations at the MFMU Network. In addition, the candidate will seek formal feedback from his mentors on these issues during quarterly meetings.

Finally, through involvement in the MFMU Network and whilst developing the 2<sup>nd</sup> project, Dr will increase his knowledge of the structure and functioning of multi-center research collaborations. The award will create the opportunity for Dr to increase his activity within the Center for Women's Reproductive Health (CWRH) in the Department of Obstetrics and Gynecology. The CWRH houses site of the NICHD MFMU Network. Dr already attends weekly CWRH research meetings during which various MFMU network projects as well as other departmental projects are discussed. He will attend quarterly meetings of the MFMU Network at the NICHD to discuss progress on the proposed factorial trial concept. He will become familiar with operational issues of the MFMU Network multi-center framework. Furthermore, during the award period he will conduct important secondary analyses based on network research data thereby improving his manuscript writing skills and generating data for future research studies and grant applications (See letters of support from Network - .ing Center).

### C. CAREER DEVELOPMENT/TRAINING ACTIVITIES

The activities needed to accomplish the candidate's specific objective have been discussed above for each objective. The candidate in consultation with his mentors identified pertinent didactic training topics and practical experience opportunities. An overview of activities during the award period and a timeline are now provided. Some of the specific didactic courses and workshops have already been identified and are included in the sections below. Others will be identified during the course of the award. Because the candidate has previously acquired basic training in some of these areas, emphasis is being given to focused, intensive advanced courses, seminars and workshops of 3-7 days duration on each of the areas of need with particular emphasis on clinical trials. In addition, formal graduate courses specifically covering metaanalysis and cost-effectiveness analysis (3 credit hours each) will be taken. Several of the advanced clinical trial concepts included in the candidate's didactic plan are covered as part of semester-long courses offered in the School of Public Health. Thus, apart from focused certificate short courses, the candidate has the option of designing a tailored program to take only relevant portions of established graduate courses at

1. Courses and Workshops: Courses in the key topical areas outlined below will be undertaken.

a) Clinical trials didactic training

- Overview of advanced methods in clinical trials (Year 1)
- Design and analysis of factorial trials (Year 2)
- Design and analysis of cluster randomized trials: "Design and analysis of cluster randomized trials in health research" course offered at the Annual Meeting of the American College of Epidemiology (Year 1)
- *Interim monitoring and stopping rules for clinical trials* (Year 4);
- Prospective alpha spending in clinical trials with multiple endpoints (Year 2 or 3);
- Advanced survival analysis methods for clinical trials (Year 3 or 4)
- Advanced logistic regression methods for clinical trials (Year 2 or 3)
- Data safety and monitoring boards (Year 2);

b) Training in Metaanalysis of clinical trials:

- School of Public Health – 3 semester credit hour course on metaanalysis (Year 1)

c) Training in Cost-effectiveness analysis:

- School of Public Health – 3 semester credit hour course on cost-effectiveness analysis (Year 4)

Principal Investigator/Program Director (Last, First, Middle):

d) Training in grant-writing and extra-mural funding:

- Junior Faculty Development Workshop – short course in Aspen, Colorado organized in collaboration with the NICHD (Year 1)
- Essential techniques in grant writing (Year 4);
- faculty development seminars

e) Communication of research findings:

- Manuscript preparation techniques (Year 1)
- Advanced communication skills for the researcher (Year 2);
- Data presentation techniques (Year 3)

f) Conduct of multi-center research

- Issues in multi-center studies (contractual arrangements, multiple PI leadership plans and resource sharing (Year 2 or 3).

Other educational resources such as Society for Perinatal Epidemiology (SPER), and NIH workshops will also be explored to attain these objectives. Registration for 2 relevant advanced statistical courses at the or other reputable school of Public Health will be undertaken.

2. Practical research activities: These are evident in the detailed description of the clinical trials provided in the research plan section of this application. Additional activities are considered in the activity timeline below and include:

- Conduct of a metaanalysis and authorship of a related manuscript
- Conduct of a cost-effectiveness analysis and authorship of a related manuscript
- Comprehensive review of antibiotic-microbial interactions and pregnancy outcomes, design/conduct of pilot studies and manuscript preparation
- Pertinent secondary analyses of research databases of our department as well as those of the NICHD MFMU Network with preparation of manuscripts.
- Presentation of research data at scientific meetings.

3. Clinical Activities: A minimum of 75-80% of time will be spent in direct research and training activities necessary to accomplish the objectives outlined in this award application. A portion of the remaining 20% time will be spent in clinical activities at Such clinical activity may be incidental to, or necessary for the proposed research projects. In addition, after completing his fellowship, [ ] will become eligible for board certification in Maternal-Fetal Medicine by the American Board of Obstetricians and Gynecologists. He must collect a case list and oral board exam during the 2<sup>nd</sup> or 3<sup>rd</sup> year of the award. Taken together this clinical activity will involve on average 1-2 half-days out of the 10 half-days per 5 day work week. It will involve clinic coverage or coverage of labor and delivery (where patients will be enrolled for both proposed projects). Therefore, overall 20% or less of the candidate's time will be spent in other activity throughout the award period (see letter of institutional commitment). These activities are essential for the candidate to be able to acquire and maintain the board credentials and privileges which are important for full participation in the conduct of clinical research.

**D: TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH:** To be able to conduct research at [ ] has completed mandatory annual IRB training covering topical areas in the ethical conduct of research over the past 3 years: the candidate completed 4 credits of initial IRB training in 2005 and subsequently has completed 1.5 credit hours of IRB training each year. The candidate has recently completed re-certification for 2008 after undergoing interactive training provided by the [ ] IRB (see Appendix B for current certificate of training). [ ] will continue to undergo these 1.5 hours of continuous education annually during the award period. The workshop he plans to take on Data Safety and Monitoring Boards will also provide additional relevant training. Finally, he will take an additional course every other year (beginning with the first year) that focuses on additional topical areas of ethical conduct of research such as conflict of interest, responsible authorship, handling research misconduct and research in international settings. The latter topic is important

Principal Investigator/Program Director (Last, First, Middle):

given the applicant's interest in conducting international multi-center studies. In the third year of the award, the applicant will attend the highly regarded "Certificate course in ethical issues in International Health Research" at the Harvard School of Public Health, Boston, designed specifically for international researchers, and addressing issues and controversies predominant in developing country settings. The course is highly recommended by prior K-awardees in our department.

**Table 1. Career development activity timeline from 1/2008 (chart):**

Training Activity	Year 1	Year 2	Year 3	Year 4	Years 5
Didactic training in clinical trials (courses and workshops)	X-X-X-X	O-X-O-X	O-X-O-X	O-X-O-X	O-X-O-O
Attendance/presentations at scientific meetings	O-O-X-O	X-O-X-O	X-O-X-O	X-O-X-O	X-O-X-X
Clinical trials planning and implementation	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X
Metaanalysis training	O-O-X-X	X-X-O-O	O-O-O-O	O-O-O-O	O-O-O-O
Cost-effectiveness analysis training	O-O-O-O	O-O-O-O	O-O-O-O	O-O-X-X	O-O-X-X
Review/pilot studies antibiotic-microbial interaction	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X
Planning cluster randomized trial	O-O-O-X	O-X-O-X	O-O-O-X	O-X-O-X	O-O-O-X
Training in grant-writing and extra-mural funding	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X
Training in communication of research findings	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X
Multi-center collaborative research training	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X	X-X-X-X
Responsible conduct of research	O-X-O-X	O-O-O-X	O-X-O-X	O-O-O-X	O-X-O-X
Clinical activity	O-X-O-O	O-O-O-X	O-O-X-O	O-O-X-O	O-O-X-O

*Key: X = Activity is ongoing during part or all of 3-month period, O = Activity NOT ongoing during entire 3-month quarter. All 3-month periods are presented chronologically.*

**2. STATEMENT BY SPONSORS, CONSULTANTS AND CONTRIBUTORS**

The Department of Obstetrics and Gynecology has established a highly successful track record of conducting research and training in maternal and perinatal care. This track-record is reflected in the department's rank ranging from 1<sup>st</sup> to 4<sup>th</sup> among US university departments of Obstetrics and Gynecology from 2000-2005 (last reported). It is also reflected by the productivity of the faculty, many of whom trained here. Dr. [redacted] is following this proven pathway and this patient-oriented research career development award request proposes a program to for him to gain advanced expertise in the conduct of clinical research of global impact, with specific emphasis on complex clinical trials addressing the major causes of obstetric and perinatal morbidity and mortality in the US and elsewhere. His overlapping areas of interest include clinical and operative obstetrics and health outcomes associated with obstetric and perinatal infections. His proposed mentors, Dr. [redacted] and Dr. [redacted], both MFM clinician scientists on our faculty, together are two of the most qualified individuals in these areas (see biosketches). They will provide structured mentorship to [redacted] so that he can take full advantage of the incredible opportunities available for his career development both university-wide at [redacted] and at the NICHD-MFMU Network as outlined in this application.

Three sealed letters of Recommendation are being provided by the following individuals:

- i) [redacted], MD: Chair Dep't of Obstetrics & Gynecology,
- ii) [redacted], MD: Professor of Ob/Gyn, [redacted], and [redacted], Dep't of Obstetrics & Gynecology,

iii) MD, MSPH: Professor and MFM Fellowship Director,

Below we provide an overview of each mentor's qualification followed by a statement from the mentor.

## 2.1 PhD, MD (MENTOR)

is a Professor and Vice-Chairman in the Department of Obstetrics and Gynecology, and Director of the Division of Maternal-Fetal Medicine at . His career research interest relates to obstetric infections including infectious etiology of preterm birth and he has published extensively in this area. He has received continuous extramural funding for nearly 20 years including over 25 grants and contracts mainly as principal investigator for studies that have included several clinical trials and observational studies (relevant to Dr. application).

was the Principal Investigator for the recently completed " that was funded by a contract with the NICHD. He was the principal investigator of the recently completed NICHD R01 "Interconceptional Antibiotics to Prevent Preterm Birth" (R01 HD ). has previously served as the Principal Investigator for the NICHD Maternal-Fetal Medicine Units Network and currently serves as the alternate PI for this Network. He was the Project director for the recently completed randomized trial of antibiotics to prevent preterm birth in fetal fibronectin-positive women conducted by the NICHD MFMU Network. He was the principal investigator for Project IV of the Perinatal Emphasis Research Center study (PERC IV, P01 HD ) that was an extensive study of the relationship between infection/Inflammation and neonatal outcome among a cohort of infants delivered between 24 and 32 weeks' gestational age. He was also the PI for the recently completed (NICHD R01 1HD0 ) long-term neurodevelopment follow-up of infants from the PERC IV study. He was also the principal investigator for the only clinical trial of azithromycin-based extended-spectrum antibiotic prophylaxis and the background observational studies. is the Founder and has served as the Director of the Obstetrics and Gynecology Laboratory for Research in Women's Health (formerly known as the OB-Gyn Infectious Disease (OBID) Research Laboratory) since its creation in 1990. The LRWH supports many ongoing research projects largely targeted toward the relationship between infection and adverse pregnancy/infant outcomes and has served as a reference laboratory for numerous multi-center national and international investigations.

### Statement:

It is with great delight that I support Dr. 's "Career Development Award in Obstetric and Perinatal Clinical Research" K-23 application. Briefly, this exceptional applicant is a young scientist with a superb educational background and outstanding analytic skills who, with the kind of career impetus provided by a development award of this nature, will undoubtedly become a leading scientist in his chosen field.

joined the Division of Maternal-Fetal Medicine, which I head, as a fellow in 2005; our top-ranked candidate for that year. He has since established himself within the department as a bright clinician and teacher, receiving recognition for excellence in medical student education as also demonstrated an outstanding potential for research productivity and a high level of achievement. Key projects on which we have worked together form the basis for key objectives he plans to accomplish with the K-23 award:

Antibiotic – Microbial Interactions and Pregnancy Outcomes: Under my supervision, completed a difficult secondary analysis of a clinical trial of interconceptional antibiotics among women at high risk for premature birth (I was principal investigator for the primary study). Three abstracts arising from that study were accepted for presentation at the annual meeting of the Society for Maternal-Fetal Medicine (SMFM) last year, one of them as a prestigious oral plenary presentation (in total presented 5 abstracts at that meeting). From that project he first-authored 2 manuscripts with input from a group of senior faculty - the first one, on the impact of antibiotics on the endometrium, was a fast-tracked publication in the *American Journal of Obstetrics and Gynecology*. The second paper presenting findings suggesting that antibiotics may interact with specific genital tract microbes to increase adverse pregnancy outcomes was an "Editor's Choice" publication in the same journal. As one of his secondary objectives, plans to conduct a comprehensive review on this issue and design pilot studies to further investigate this hypothesis, which may lead to new avenues for preventing preterm birth and pregnancy loss. This may form the basis for a future R-01 application. I will provide the needed mentorship for him to achieve this objective and make the resources of my laboratory available to him for support.

Principal Investigator/Program Director (Last, First, Middle):

Strategies for Optimizing Antibiotic Prophylaxis for Cesarean Section: More recently, still under my mentorship [redacted] conducted an analysis and first-authored a manuscript presenting the salutary impact of Azithromycin-based extended-spectrum antibiotic prophylaxis on post-cesarean endometritis. These findings are published in the January 2008 edition of *Obstetrics and Gynecology*. He also presented an abstract at this year's SMFM meeting reporting on the impact of extended-spectrum prophylaxis on wound infections (in all he presented 4 abstracts at this meeting including one oral). This project was a follow-up to prior studies including a clinical trial of the impact of extended-spectrum prophylaxis for which I was principal investigator. All these formed the basis for [redacted] successful presentation of the factorial trial concept for study within the MFMU Network, a concept I co-sponsored with him. The process of developing and conducting this study will help Dr. [redacted] accomplish his primary objective of gaining advanced training and experience in the conduct of clinical trials.

MFMU Network and Career Development: I will serve as Dr. [redacted] his Co-PI for this network project and mentor him on his role as principal investigator for this specific network project. Sites are formally allowed to have one K-award affiliated with the MFMU Network and this award will be consistent with that stipulation. The resources of the network including senior investigators from the clinical sites and the NICHD as well as the resources of its Biostatistical Coordinating Center will be invaluable to [redacted]. I find it hard to imagine a more ideal scenario for any candidate's career development.

In addition to the above [redacted] has conducted other projects and authored other peer review publications, and at his leisure begun to provide research mentorship for residents within the department. All these I believe "speak volumes" regarding his solid scientific background, quality work and commitment to academic work and health care research.

Need for K-Award: I have discussed [redacted] unique academic career plans at length with him. He wants to apply his maternal-fetal medicine training and strong background in research methods to maternal and perinatal health care issues of global relevance – here in the United States and elsewhere. He will certainly be one of only a few U.S. physicians with his kind of high-level training to have these interests. [redacted] Department of Obstetrics and Gynecology harbors both a Maternal-Fetal Medicine Division which is highly productive in Obstetric and Perinatal research, and a strong International Health Division, and therefore provides the ideal nurturing environment for him. He wants to be involved in the generation of "best evidence" through clinical trials. It is obvious that to become an independent investigator in this area he needs additional training and experience. In particular, [redacted] will benefit from increased experience in practical problem solving during the implementation and conduct of clinical trials. This experience will include overcoming obstacles/barriers to successful trial conduct and completion with emphasis on compromises necessary to successfully complete clinical trials while simultaneously preserving the integrity and quality of the trial. This experience will be of immense value for the development, implementation and conduct of single- and multi-center trials both within the US and internationally setting. This award would afford time away from clinical duties and enhance logistical support needed for him to use the available mentorship resources to achieve his goals. He has the full backing of the department.

My extensive experience in the successful conduct of clinical studies (both single and multi-center, interventional and observational), 24-year experience in the practice of obstetrics (20 years in Maternal-Fetal Medicine), successful mentoring of hundreds of residents, fellows, graduate students and faculty (see below for just a selection of my mentees which includes career development and training grant awardees), and career-long commitment to improving outcomes related to obstetric and perinatal infection make me well-qualified to be Dr. [redacted]

[redacted] mentor with overall responsibility for ensuring the candidate's career development as outlined in this K-23 application.

I will devote time to promote his ongoing research and to provide guidance as outlined above. Specifically, as the MFM Division Director, I pledge to ensure that [redacted]'s research time is fully protected as outlined in this application (because our faculty pool is relatively large and stable clinical coverage is not a problem). Dr. [redacted] research progress will be monitored through our weekly Divisional Research Meetings attended by both myself

Principal Investigator/Program Director (Last, First, Middle):

and In addition, Dr: will coordinate with Dr and me to and convene quarterly meetings to appraise his overall progress.

Below are publications that have resulted at least partially as a result of my mentorship. I have underlined the mentees, and provided in parentheses their academic level at the time of my mentoring. See Table 2 for details concerning these mentoring.

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Principal Investigator/Program Director (Last, First, Middle):

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Table 2. Selection of Mentoring Relationships:

Faculty Member (Last, first, Degree)	Past / Current	Trainee Name	Status (Post)	Degree (Pre)	Training Period	Research Topic
	Past			MD	1991- 1993	Obstetrical Infections & Preterm Birth
	Past			MD	1992- 1992	Obstetrical Infections & Preterm Birth
	Past			MD	1992- 1994	Obstetrical Infections & Preterm Birth
	Past			MD	1994-	Obstetrical Infections & Preterm Birth
	Past			MD	1994-96	Preterm birth, clinical obstetrics
	Current			MD	1995 -	Obstetrical Infections & Preterm Birth
	Past			MD	2001- 2004	Obstetrical Infections & Preterm Birth
	Current			MD	1998 -	Obstetrical Infections & Preterm Birth
	Current			MD	1999- 2005	Perinatal infections
	Current			MD	1999 -	Obstetrical Infections & Preterm Birth
	Current		Instructor/F ellow	MD, PhD	2005-	Obstetrical Infections & Preterm Birth
	Past		Med-Peds Physician	BS	1994	Obstetrical Infections & Preterm Birth
	Past		ID Investigator	PhD	1999- 2003	Obstetrical Infections & Preterm Birth
	Past		Asst. Prof	PhD	2003- 2006	Obstetrical Infections & Preterm Birth
	Past		ID Investigator	BS	2003- 2006	Obstetrical Infections & Preterm Birth
	Current		Graduate Student	BA	2003 -	Preterm Birth & Long- term Neuro-outcome

## 2.2. , MD, MSPH (CO-MENTOR)

Dr. is Professor of Obstetrics and Gynecology at the University of School of Medicine, Director of the Center for Women's Reproductive Research (CWRH), and Principal Investigator of the NICHD Maternal-Fetal Medicine Units (MFMU) Network. He has a secondary

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Principal Investigator/Program Director (Last, First, Middle):

the annual meeting of the Society of Maternal-Fetal Medicine and co-authored a chapter entitled "

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Table 3. Details of most substantive mentoring relationships.

Faculty Member (Last, first, Degree)	Past / Current	Trainee Name	Status (Post)	Degree At Entry	Training Period	Research Topic
	Current			MD	1998-	Cost Effectiveness Analysis Decision Analysis Vertical HIV Transmission
	Current			MD, MSPH	1998-	Perinatal Clinical Trials
	Current			MD	2000-	Outcomes Research Reproductive Tract Infection
	Current			MD	2000-	Patient Oriented Research
	Current			MD	2000-	Patient Oriented Research
	Past			PhD, MD	2002-05	Clinical Perinatal Epidemiology
	Past			MD	2002-05	Patient Oriented Research
	Current			MD	2003-	Perinatal Research
	Past			MD, MSPH	2003-07	Patient Oriented Research
	Current			MD, PhD	2005-	Obstetric, Perinatal & Global Health Research

### 2.3. Letters of Support from other Contributors/Consultants

Letters of support from the following contributors are included in the ensuing pages:

i.

J Network

D)

Network

Biostatistical Center).

CHD MFMU

iii. :

iv. |

v. |



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

February 4, 2008

Center for Scientific Review  
National Institutes of Health  
Bethesda, Maryland

Dear Reviewer:

This letter is written to support the application of \_\_\_\_\_ or a K-23 award entitled "Career Development Award in Obstetric and Perinatal Clinical Research". I am delighted to confirm that the second research project he proposes to implement – Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) Study – was approved by the steering committee of the NICHD Maternal-Fetal Medicine Units (MFMU) Network for further development as a network study concept on January 11<sup>th</sup>, 2008.

\_\_\_\_\_ is affiliated with the MFMU Network as an investigator with the Department of Obstetrics and Gynecology of the University \_\_\_\_\_, one of the 14 MFMU Network Centers. This Cooperative Network consists of a team of academic clinical centers and a data coordinating center (The George Washington University Biostatistics Center, BCC), as well as the National Institute of Child Health and Human Development, that have agreed to investigate problems in clinical obstetrics in a collaborative manner. The clinical centers represent premier institutions in perinatal medicine with track records of excellence in clinical research, and the cooperative agreement mechanism provides an infrastructure by which multidisciplinary staff can efficiently develop and implement multiple, complex, research projects simultaneously and disseminate information and research results. Dr. \_\_\_\_\_ colleagues therefore have the unique opportunity to further develop the factorial trial concept within the framework of the network, with the assistance of Biostatisticians at the coordinating center as well as input from the experienced team of network clinical investigators. The next steps in the process will involve the development of a mini-protocol for discussion & approval, followed by a full protocol. All protocols prioritized and activated are funded by the NICHD.

\_\_\_\_\_ research activity within the network also includes a recent study of the timing of elective repeat cesarean delivery and its impact on neonatal outcomes. He presented the findings during an oral session at the Annual Meeting of the Society of Maternal-Fetal Medicine in Dallas, Texas, earlier this month. The study generated a lot of interest and will likely have a high impact on perinatal care. A manuscript first-authored by the candidate is ready for submission to *JAMA*. Thus, the network provides additional opportunities for \_\_\_\_\_ research career development including familiarization with the operational issues involved in multi-center research. I believe a K-23 award will be perfect for the applicant's career development.

Sincerely,

P

rk



SCHOOL OF  
MEDICINE

Department of Obstetrics and Gynecology

February 5, 2008

Center for Scientific Review  
National Institutes of Health  
Bethesda, Maryland

To Whom It May Concern:

I am writing in support of [redacted] application for a K-23 award entitled "Career Development Award in Obstetric and Perinatal Clinical Research". As Director of the Center for Women's Reproductive Health at the University of [redacted], I have had the pleasure of working with Dr. [redacted] on several research studies published in the *American Journal of Obstetrics and Gynecology* last year. One of the studies, concerning the impact of [redacted] was chosen for presentation in the Fellows Plenary Session at the Society for Maternal-Fetal Medicine Annual Meeting. Our data team is currently working with [redacted] on several additional papers to be published this year.

As an epidemiologist, [redacted] brings a strong methodological approach to his clinical research. His studies are well designed and implemented, with clearly developed apriory analysis plans. He works extremely well collaboratively with our team, whose mission it is to provide data management and analysis support to Center faculty.

As part of his proposed research initiatives, [redacted] will be conducting a 3-arm trial of oxytocin regimens to prevent obstetric hemorrhage. Our data management team has participated in discussions concerning study design for this project. We also look forward to assisting Dr. [redacted] in preparing appropriate data collection instruments, designing a data system specific to this project, providing data management over the course of data collection, and preparing a final analysis dataset. Under his supervision, we will also provide data analysis support for this project.

I strongly recommend [redacted] for this K-23 award. He has already been remarkably productive during his fellowship, having made important contributions to the literature on several topics. I believe he has outstanding potential as a clinical researcher, and this award would help him achieve that potential.

Sincerely,

To Whom It May Concern:

Higher Doses vs. Low Dose  
Birth C

I am delighted to write this letter in support of \_\_\_\_\_ application for a career development award. The Investigational Drugs Pharmacy of the University of \_\_\_\_\_ will support \_\_\_\_\_ and the Department of Obstetrics and Gynecology in conducting the above IRB-approved 3-arm clinical trial. We are currently working out the details for this pharmacy to procure, label for blinding, store and dispense all three strengths of oxytocin.

Our pharmacy has a strong track record for providing university-wide support for clinical trials and other studies. We recently supported the participation of the department of obstetrics and gynecology in the conduct of the "BEAM trial" within the Maternal-Fetal Medicine Units Network to evaluate the potential of magnesium sulfate to prevent the occurrence of cerebral palsy or perinatal death. \_\_\_\_\_; also informed us that he is proposing a trial of antibiotic prophylaxis regimens for cesarean section within the network. We are available to participate in this study as well and look forward to a long productive research relationship with \_\_\_\_\_ and colleagues in the department.

Yours sincerely,

Department of Pediatrics  
Division of Neonatology

February 8, 2008

K-23 Review Committee  
Center for Scientific Review  
National Institute of Health  
Bethesda, Maryland

Re:

Dear Committee Members:

I am pleased to write this letter in enthusiastic support of [redacted] application for a K-23 Patient-Oriented Research Career Development Award. I have known and interacted with [redacted] over nearly 3 years, since he joined the Department of Obstetrics and Gynecology here at [redacted] as an Instructor and Fellow in Maternal Fetal Medicine. These interactions have occurred within the context of the close academic and clinical collaboration that the Divisions of Maternal Fetal Medicine and Neonatal-Perinatal Medicine (which I direct) share in taking care of babies of high-risk pregnancies and their mothers. Besides routine clinical work on labor and delivery, we hold a common MFM/Neonatology Fellows' Conference and a Perinatal Morbidity and Mortality Conference each on a monthly basis. Both divisions recently held a retreat during which we explored areas for common research initiatives. In addition to being UAB's site Principal Investigator for the NICHD Neonatal Research Network, I also serve as a consultant to the local site of the NICHD Maternal-Fetal Medicine Units Network.

I have observed [redacted] to be a very hard working and dedicated academician with well-researched presentations during conferences. A review of his background, research activity and publications leaves no doubt that he has incredible potential to become a leading scientist in his chosen area of maternal and perinatal health. Our common interests extend to global health issues; he is a consultant on our grant application to continue as a site for the Global Network for Women's and Children's Research. I have also guided him in developing an evidence-based strategy for improving maternal and perinatal health in Cameroon to be evaluated through a cluster randomized trial. I am therefore glad to have the opportunity to continue to work with [redacted] as he remains on faculty here at [redacted]

The University of [redacted]

This K-23 award is an essential ingredient for career development; it will provide protected time over a prolonged period and additional resources in order for him to develop as an independent investigator. . . . consulted me while designing neonatal outcomes for his proposed trial on cesarean antibiotic prophylaxis strategies. I remain available to provide a neonatology perspective as he continues to develop this study. Once more I would like to express my profound support for this candidate's application.

Sincerely,

The University of .

### 3. ENVIRONMENTAL AND INSTITUTIONAL COMMITMENT TO THE CANDIDATE

The University of \_\_\_\_\_ and its department of Obstetrics and Gynecology provide an outstanding academic and research environment with the infrastructure and personnel needed to facilitate and optimize \_\_\_\_\_ career development. At the time of the award \_\_\_\_\_ will be an assistant professor within the department's Maternal-Fetal Medicine and International Health Divisions and its Center for Women's Reproductive Health (which houses both \_\_\_\_\_ site for the NICHD MFMU Network and the US site for its major international research center, CIDR (Center for Infectious Diseases Research in \_\_\_\_\_). The main academic resources available to \_\_\_\_\_ have been outlined in the statements of his mentors and the letters of support. This section provides details about these and other resources within the \_\_\_\_\_ academic environment. \_\_\_\_\_ commitment to the candidate is also described below.

#### A. Description of Institutional Environment

**The University of \_\_\_\_\_ (\_\_\_\_\_ President)** founded in 1969, is a comprehensive urban university with a strong medical center with annual revenues of \$1.5 billion (2004). Currently, over 18,000 students are enrolled in 12 schools and 138 degree programs \_\_\_\_\_ has grown rapidly from its beginnings only 38 years ago in large part due to a strong commitment to research. External grant support at \_\_\_\_\_ has doubled every decade, from \$18 million in 1969 to over \$460 million today \_\_\_\_\_ ranks in the top 20 overall in NIH funding in the US, with five schools (including the Schools of Medicine and Public Health) ranking in the top 20 and four departments ranking in the top five (Ob/Gyn 1<sup>st</sup> to 4<sup>th</sup>). Both the University and the Medical Center house a number of special interdisciplinary centers, focusing on specific relevant research areas including the Center for Research in Women's Health within the Ob/Gyn department. In addition the Institutional Review Board of the University which reviews thousands of local, multicenter and international projects conducted within various units of \_\_\_\_\_ provides training in the responsible conduct of research and will be a resource to \_\_\_\_\_ s. Also, a multitude of relevant professional development courses on topics such as grant-writing, public speaking, and presentational techniques are offered by the career development office of the University as well as various departments within the university.

**The Department of Obstetrics and Gynecology (\_\_\_\_\_ Chair) in The \_\_\_\_\_ School of Medicine (\_\_\_\_\_ )** is comprised of 40 full time MD faculty, two PhD faculty and scores of supporting staff dedicated to the medical care of women through teaching, patient care, and research. The department is recognized internationally for its research, reflected in its top 5 ranking among U.S. Departments of Obstetrics and Gynecology in receipt of NIH research support for the past 8 years. The Department's broad research scope encompasses a great deal of basic biomedical research, translational research, large-scale clinical trials, as well as epidemiologic research. This research is generally integrated and managed within the **Center for Women's Reproductive Health (\_\_\_\_\_ Director)**. The center is one of the key sites of the NIH sponsored Maternal Fetal Medicine Units Network (MFMU) at the forefront of discovery in obstetrics (see below). There is an impressive range of research resources directly available to Dr \_\_\_\_\_ including research support staff, data programmers and analysts, secretarial assistance, grant administrators, IRB manager and several research nurses. The Department of OB/GYN is organized into seven divisions, which includes the **Maternal-Fetal Medicine Division (\_\_\_\_\_ Director & Vice Chair)**. Dr. \_\_\_\_\_ is joining 11 full-time Maternal-Fetal Medicine faculty members, the majority of whom are actively engaged in research. This research activity in the division is accorded the utmost importance – a weekly review meeting during which new research concepts are also discussed is held every Friday under the direction of the department chair, Dr. \_\_\_\_\_. This research meeting has approved both projects proposed by \_\_\_\_\_. There is strong intra-departmental statistical support, with a Biostatistical unit headed by \_\_\_\_\_ (see letter of support). This unit includes 2 biostatisticians, a data manager, a data analyst and programmer. Several faculty members within the department have successfully launched their careers with NIH funded training grants including K-01, K-23, the WRHR and the BIRWCH. As discussed below Dr. \_\_\_\_\_ is a recent K-23 award recipient who has transitioned from fellow to \_\_\_\_\_ full professor, independent investigator and head of a highly productive research and service organization. His mentors included those in the current application.

Principal Investigator/Program Director (Last, First, Middle):

**The Maternal-Fetal Medicine Units (MFMU) Network (Catherine Y. Spong, Program Director and Program Scientist) and UAB:** The National Institute of Child Health and Human Development (NICHD) created the Maternal Fetal Medicine Units (MFMU) Network in 1986 to focus on clinical questions in maternal fetal medicine and obstetrics. Operating under cooperative agreements, the current Network is comprised of fourteen university-based clinical centers (including [redacted] and a data-coordinating center. The purpose of the MFMU Network is to conduct perinatal studies to improve maternal and fetal outcomes. Greatest emphasis and priority are given to randomized-controlled trials. More than 35 randomized clinical trials, cohort studies and registries have been completed or are in progress.

The 14 MFMU Network academic clinical centers, the data-coordinating center and the NICHD have agreed to investigate problems in clinical obstetrics in a collaborative manner. The clinical centers represent premier institutions in perinatal medicine with track records of excellence in clinical research

[redacted] The data-coordinating center was selected on the basis of their experience with the coordination of multi-center clinical trials, and with proven expertise in study design, data management and biostatistical analysis. The current data-coordinating center for the Network is The George Washington University Biostatistics Center (BCC; **Elizabeth Thom, Principal Investigator**). The cooperative agreement mechanism provides an infrastructure by which multidisciplinary staff efficiently develop and implement multiple, complex, research projects simultaneously and disseminate information and research results. Overall program management and stewardship responsibility for review and oversight of the cooperative agreement resides with the NICHD. However, additional governing bodies provide in-depth scientific evaluation and support of the program. The MFMU Network is overseen by three governing bodies (Steering Committee, Data and Safety Monitoring Committee (DSMC) and the Advisory Board). Details concerning the specific role of the network in fostering [redacted]'s career goals are presented in the letters of support from the Program Scientist and from the PI of the biostatistical center as well as from his mentors.

The Department of OB/GYN's global health emphasis is strongly reflected in its founding of the **Center for Infectious Disease Research in [redacted] (Director)** with five [redacted] ob/gyn faculty as well as other medical specialists and administrative support staff living full time in [redacted]. The [redacted] is a formally constituted NGO, a collaboration between the [redacted] government and the University of Alabama at [redacted]. Dr [redacted] is also director of the department's international division. In its first six years, [redacted] has grown rapidly and now has over 400 staff and an active service and research portfolio of more than 20 projects with grant income in excess of \$20 million. [redacted] will receive over \$20 million in grant income for 2008 mostly from the U.S. government (CDC, NIH, USAID) as well as from the Bill and Melinda Gates Foundation, Columbia University MTCT Plus Initiative and The *Elizabeth Glaser Pediatric AIDS Foundation*. [redacted] represents an opportunity for future multinational obstetric and perinatal research collaboration. It is also noteworthy that the remarkable growth of [redacted] highlights the success of mentoring within [redacted] Department of Obstetrics and Gynecology: Dr [redacted] who is both a product of and catalyst of this growth was a resident and fellow in international health. He is a past recipient of a K-23 award with both Dr [redacted] and Dr [redacted] among his mentors.

Resources within **other departments and centers in the School of Medicine** are available to [redacted] as well. Prominent among these is the Division of Neonatal/Perinatal Medicine in the Department of Pediatrics, which naturally maintains a strong relationship with our Division of Maternal Fetal Medicine. Headed by [redacted], this division is one of the centers of the NICHD's Neonatal Research Network. [redacted] is a consultant to [redacted] site for the MFMU network and he will be an important resource in determining appropriate perinatal outcomes.

**The [redacted] School of Public Health (SOPH) (Dean)** ranks 11<sup>th</sup> in NIH funding with over \$28 million annually in Grants Research. The SOPH has 22 programs of study and six departments (Biostatistics, Environmental Health Sciences, Epidemiology and International Health, Health Behavior, Health Care Organization and Policy, and Maternal and Child Health). The School also supports five centers that play key roles in its mission to prevent and control diseases including the [redacted].

Principal Investigator/Program Director (Last, First, Middle):

**Health.** Both the departments of Biostatistics ( , Chair) and Epidemiology (: , Chair) have strong collaborative relationships with the department of obstetrics and gynecology. In fact one of our PhD-level statisticians shares a joint appointment with the department of biostatistics. A large multi-center randomized trial of cerclage in the setting of short cervix is currently ongoing within the department. Statistical analysis will be performed under the auspices of and the biostatistics department of the school of public health.

**B. Institutional Commitment to the Candidate's Research Career Development**

The institutional commitment document provided by the Chair of the Department of Obstetrics and Gynecology. is attached on the next page.

February 8, 2008

RE: \_\_\_\_\_ MPH, PhD

Dear Review Committee Members:

I am pleased to support \_\_\_\_\_'s K23 application. As per my letter of reference, \_\_\_\_\_ has a long standing commitment to women's reproductive health care research and at a university academic center in the United States. He has acquired skills and knowledge that reflect his outstanding and original academic productivity to date. Dr. \_\_\_\_\_'s K23 will allow him the protected time and resources to obtain expertise and accomplish research in this area of his excellent career development plan. That area is the conceptualization, development, accomplishment, analysis, and publication of large randomized, double-blind single center, multicenter, and international clinical trials on very important women's reproductive health care issues. The Division of Maternal-Fetal Medicine and the Department of Obstetrics and Gynecology at \_\_\_\_\_ are well known for expertise in these areas. We have an extensive record of accomplishing large NIH clinical trials at our university, in multicenter institutions supported by the NIH in the United States and in international trials. Dr. \_\_\_\_\_ mentors are the \_\_\_\_\_ leaders in our Maternal-Fetal Medicine Division in these research areas. Our mentors are committed to Dr. \_\_\_\_\_ success and have devoted immense time to the development of the two described research plans within his K23 application.

\_\_\_\_\_ will complete his Maternal-Fetal Medicine fellowship on June 30, 2008. We have previously offered him a faculty position as a tenure track full-time assistant professor and with an appreciable salary commensurate with his Maternal-Fetal Medicine expertise that is not contingent upon the receipt of this K23 award. The K23 award will allow us to guarantee that Dr. \_\_\_\_\_ will have a minimum of 75% fully protected time to accomplish his career development plan and his research. In our department a Maternal-Fetal Medicine assistant professor usually commits 75% of their time to clinical and educational duties. Dr. \_\_\_\_\_'s 75% protected time will not detract from our department duties. In the fall of 2007 our department recruited three additional OB/GYN generalists, two of which have been assigned to cover routine obstetric services. We now have six generalists, 12 Maternal-Fetal Medicine specialists, and 4 Maternal-Fetal Medicine fellows available to cover our service, educational and research missions. We again confirm that Dr. \_\_\_\_\_ will have at least 75% protected time and more, if required, to accomplish his career development, plans, and research projects.

Dr. \_\_\_\_\_ will continue to have an appropriate office, computer support, and especially the support of our departmental biostatistics division in regard to utilization of our large perinatal databases and perinatal sample collections for many of his projects, not just

RE:  
February 8, 2008  
Page 2

the two listed within this application. He will have sufficient financial support and research nurse assistance to accomplish the two research plans included in his application. One plan will be largely supported through the NICHD Maternal-Fetal Medicine Units Network, and the other will be funded within our department. Drs. [redacted]'s primary mentors, have appreciable protected time (a minimum of 50%) for their research and for their mentoring of our more junior faculty fellows in our Maternal-Fetal Medicine Division of our department.

In summary, Dr. [redacted] has the unequivocal support of our department in regard to his recruitment as a tenure track assistant professor with full academic faculty privileges.

Sincerely,

## 4. RESEARCH PLAN

**Introduction to Research Plan** proposes to complete two clinical trials during the award period. First, a 3-arm dose-response clinical trial of oxytocin is already IRB approved and should be completed within the first 3 years of the award period. The 2<sup>nd</sup> study – Factorial trial of antibiotic prophylaxis strategies to be conducted within the framework of the NICHD MFMU Network to which belongs, will undergo planning over the 1<sup>st</sup> 2 years. It is anticipated that enrollment would coincide with years 3-4 of the award and that analysis and reporting will be completed by year 5. These proposed studies are now described below – the use of 1 or 2 below is to identify sections which focus exclusively on one project.

### 4.1. Research Project 1: “Higher vs. Low-dose Oxytocin to Prevent Uterine Atony/ Postpartum Hemorrhage at Vaginal Delivery: A 3-Arm Clinical Trial”

**A.1. Specific aims:** Obstetric hemorrhage is the major cause of maternal mortality worldwide. Our UAB group has previously demonstrated that prophylactic high dose oxytocin (80Units/500cc) compared to standard dose (10 units/500 cc) at cesarean more effectively prevents uterine atony/obstetric hemorrhage, reducing the need for therapeutic oxytocin and other uterotonic. It is unknown whether this is applicable to vaginal deliveries as well and if intermediate doses are equally effective.

We therefore propose the following primary hypothesis: Use of higher doses of oxytocin (40 or 80 units /500cc saline) compared to standard dose (10 units/500cc) at vaginal delivery, will reduce the incidence of treated uterine atony with a positive dose response effect.

(Recall that a separate cost-effectiveness analysis will be conducted to compare these doses).

#### B.1. Background and Significance

Obstetric hemorrhage, most commonly soon after delivery, is the single most prevalent cause of maternal mortality worldwide [Ronsmans, 2006] as well as the most prevalent obstetric cause in the United States [Berg, 2003]. Uterine atony accounts for about 80% of this postpartum hemorrhage (PPH), while other causes such as genital injury, retained placenta and coagulopathy account for a minority [ACOG Practice Bulletin #76, 2006].

Multiple risk factors for PPH and uterine atony (and associated relative risks) include [Combs, 1991; Rouse for NICHD MFMU Network, 2005]: prolonged 3<sup>rd</sup> stage (OR=7.6), preeclampsia (5.0), previous PPH (3.5), twin pregnancy (2.4-3.3), arrest of descent (2.9), Asian or Hispanic ethnicity (1.7-2.4), induced or augmented labor (1.7-2.2), prolonged labor (2.2), chorioamnionitis (1.8), macrosomia > 4000gm (1.8), MgSO<sub>4</sub> use (1.8), hydramnios, fibroids, and use of uterine muscle relaxants.

Treatment options for uterine atony/obstetric hemorrhage that does not immediately respond to fundal/uterine massage include medical, tamponade and surgical modalities supplemented by blood product replacement when indicated [ACOG Practice Bulletin # 76, 2006]. Medical therapy with oxytocics or uterotonic (oxytocin, methyl ergometrine and/or prostaglandins) is effective first line treatment for uterine atony. Most hemorrhage occurs in the first 24 postpartum hours, the majority during the 1<sup>st</sup> hour. Evidence from Cochrane Reviews of clinical trials indicates that prophylactic administration of uterotonic agents at the time of delivery effectively reduces atony and postpartum hemorrhage by about 40-50% [Liabsuetrakul, 2007; McDonald S, 2004; Prendiville, 2003; Elbourne, 2001]. The number needing prophylactic oxytocic to prevent one episode of postpartum hemorrhage is only 22. Consequently, oxytocic medications are used routinely after delivery. Compared to methylergometrine and misoprostol, oxytocin has a good safety profile and induces fewer, if any, side effects [McDonald S, 1993; McDonald S, 2004; Gulmezoglu AM, 2001]. Oxytocin is therefore the first line uterotonic in the US and many other countries. Route and dose of administration of prophylactic oxytocin vary: direct intravenous (5-10 units), intravenous infusion with isotonic solution (10-40 units/liter) or intramuscular injection (10 units) [Elbourne, 2001; ACOG Practice Bulletin #76, 2006; Rouse for MFMU, 2005]. ACOG recommends avoiding direct IV administration because concerns regarding hypotension. At least one clinical trial has demonstrated no benefit to administering prophylactic oxytocin before, as opposed to after placental delivery [Jackson KW, 2001].

Although there is ample data demonstrating the prophylactic effectiveness of oxytocin, there is a paucity of information regarding the optimal dose for preventing uterine atony and postpartum hemorrhage. Available

Principal Investigator/Program Director (Last, First, Middle):

evidence suggests that higher doses of oxytocin than routinely used may be more effective. In a double-blind controlled randomized trial previously conducted by our group at UAB involving 321 women delivered by cesarean, high-dose (80 units/500cc) compared to low-dose (10 units /500cc) of oxytocin infused over 30 minutes significantly reduced the need for medically treated uterine atony (including use of additional oxytocin) by 50% (39% to 19%) [Munn, 2001]. Uterine atony requiring medical treatment with uterotonics other than oxytocin (methylergometrine and PGF<sub>2α</sub>) was reduced by nearly 80% (9% to 2%). No excess of hypotension or other side effects was observed in the higher dose oxytocin group. We now routinely use a higher dose of oxytocin of 80 units/500cc for immediate postpartum hemorrhage prophylaxis among women delivered by cesarean. Since the majority of women deliver vaginally, it is currently uncertain and important to know whether the same benefit applies to this mode of delivery. One small study suggested a dose-response to prophylactic administration of oxytocin upon vaginal delivery: 10 units of oxytocin were more efficacious than 5 units in preventing PPH [Dumoulin, 1981].

Most women undergoing vaginal delivery at our institution present at least one risk factor for uterine atony and might derive the same magnitude of benefits as those undergoing cesarean from a higher dose oxytocin regimen. Our current immediate vaginal delivery regimen consists of 10 units of oxytocin administered in 500cc of crystalloid as a bolus of over 0.5-1 hour. The purpose of this study is therefore to determine whether a higher dose (and concentration) of oxytocin at delivery of 40 U/500cc or 80 U/500cc administered as a bolus over 30 minutes is more effective than the current low dose bolus (10 U/500cc) in preventing uterine atony and its complications after vaginal delivery and whether the dose of 80U dose is more effective than the 40U dose (dose-response). All women receive a maintenance dose of oxytocin consisting of 20U in 1000cc for 8 hours. Although, the dose of 40 U/500cc is lower than the dose of 80 U/500cc utilized in the cesarean study, its concentration is nevertheless at least 4 times the commonly used doses of 5-20 U/Liter in the literature [Cochrane reviews], and twice the upper limit of the recommended dose concentration for treatment of PPH in the US (ACOG, 2006). If equally efficacious, the dose of 40 units is more likely to be acceptable to clinicians for routine prophylaxis, minimize costs and more likely to be devoid of theoretical concerns of hypotension and water intoxication than the dose of 80 units.

We propose to assess the following primary and secondary research hypotheses:

Primary Hypothesis:

i.) Prophylactic use of a higher dose of oxytocin (40 or 80 units in 500cc) compared to use of standard (low) dose concentration of oxytocin (10 units/500cc), over 30 minutes will reduce the incidence of medically treated uterine atony (additional oxytocin, methylergometrine and/or prostaglandins) and/or atony requiring tamponade, surgery or blood transfusion (adjusted for baseline hematocrit) among women delivered vaginally, with a positive dose response (by test for trend). 40U/500cc is expected to reduce this endpoint by at least a third and 80U/500 by at least 50%.

Secondary Hypotheses:

i.) Prophylactic use of higher-dose oxytocin (40U or 80U /500cc) compared to low dose oxytocin will reduce the incidence of uterine atony requiring treatment (other than oxytocin) with methylergometrine and/or prostaglandins, tamponade, surgery or blood transfusion (adjusted for baseline hematocrit) by at least \*60% among women at high-risk for uterine atony delivered vaginally. (\*There was an 80% reduction among women undergoing cesarean).

ii.) Higher-dose oxytocin is associated with a lower incidence of a  $\geq 6\%$  absolute reduction from pre- to post-delivery hematocrit (*adjusted for BMI, fluid input and time from delivery to blood draw for hematocrit [proxy for fluid intake/postpartum shifts]*).

iii.) Higher-dose oxytocin is associated with a lower incidence of a) tamponade, b) surgery, c) blood transfusion, d) clinically determined PPH > 500cc, e) lower mean reduction in pre-/post delivery hematocrit (adjusted as above), f) lower mean estimated blood loss, and g) lower incidence of endometritis.

iv.) Higher dose oxytocin is similar to low dose oxytocin in incidence of side effects including a) treated hypotension within 1 hour of delivery and b) symptoms of water intoxication – radiological evidence of pulmonary edema, shortness of breath treated with diuretics, postpartum seizures within 2 days of delivery.

**C.1. Preliminary Studies/Progress Report:** As described above the randomized trial demonstrating better efficacy of a high dose oxytocin regimen was previously conducted by the : [Munn, 2001]. Drs.

Principal Investigator/Program Director (Last, First, Middle):

who were the senior investigators on the previous project are both MFM Faculty members who have provided input to the development of the new study and remain a resource for Dr. . The department has approved this study proposed by [ ] and earmarked it for intramural funding support. Dr. has already obtained IRB approval (see appendix) and is currently in the process of having the informed consent document translated to Spanish. In addition, data collection forms are being developed in collaboration with the department's biostatistical staff (See letter of support from ). Furthermore, the Investigational Drug Pharmacists (also see letter of support from PharmD) who will be responsible for administering the randomization protocol are in the process of working out the logistics for the study. To assist with sample size estimations D. conducted a review of labor and delivery logs and pharmacy records and found that at least 15% of vaginal deliveries currently require treatment for uterine atony with current regimens for prophylaxis. Also meetings have been held with labor and delivery nursing staff and administrators as well as with clinical pharmacists to plan the trial.

#### D.1. Research Design and Methods

This is a double-masked 3-arm RCT of higher-dose (40U or 80U) vs. low-dose (10U) oxytocin each in 500cc of crystalloid administered as a bolus over 30 minutes. All patients will receive routine post-delivery maintenance oxytocin of 20U in 1 liter of crystalloid administered over 8 hours (125cc/hour).

a. Inclusion criteria: All women undergoing vaginal delivery at  $\geq 24$  weeks gestation who provided informed consent. Consent documents will be available in both English and Spanish.

b. Exclusion criteria: Cesarean delivery, precipitous deliveries (prior to consent), refusal or lack of consent, antepartum fetal demise, DIC or other evidence of coagulopathy (INR $>1.5$ , thrombocytopenia  $< 10,000$ ), pre-viable pregnancy termination or intrapartum use of concentrated oxytocin protocol.

c. Primary Outcomes:

i.) Incidence of uterine atony treated medically\* (additional oxytocin, methyl ergonovine and/or prostaglandins), surgically, by tamponade and/or requiring transfusion. Choice of medical treatment will be at the discretion of the treating physician based on institutional practice patterns, which encourage use of additional oxytocin initially (30 units), followed by methergine or parenteral prostaglandins preferentially over misoprostol. \* For all practical purposes the incidence of this primary outcome will be equal to the incidence of medically treated uterine atony as it is expected that tamponade or surgical measures would only occur after failure of medical treatment.

d. Secondary outcomes:

i. Incidence of uterine atony treated medically with uterotonics other than oxytocin (methyl ergometrine and/or prostaglandins), surgically, by tamponade and/or requiring transfusion among women at high-risk for uterine atony: defined as presence of labor induction or augmentation  $> 6$  hours, Asian or Hispanic ethnicity, chorioamnionitis, intrapartum MgSO<sub>4</sub> use, birth weight  $\geq 4000$  g, twin pregnancy, prolonged 3<sup>rd</sup> stage ( $>20$  minutes), previous PPH (requiring blood transfusion), arrest of descent /protracted 2<sup>nd</sup> stage ( $>2$  hours for primiparous and  $>1$  hour for multiparous women), hydramnios, and use of uterine muscle relaxants (e.g. terbutaline, calcium channel blockers or inhalational agents within 24 hours of delivery).

ii. Incidence of  $\geq 6\%$  reduction in hematocrit pre/post delivery (adjusted for BMI, admission-to-delivery time and time from delivery to phlebotomy). Pre-delivery hematocrit is that drawn upon admission for delivery or the most recent. Post-delivery hematocrit is that drawn within 24 hours of delivery, prior to any blood transfusion.

iii. Incidence of atony requiring any uterotonic, stratified by risk factor subgroups.

iv. Need for blood transfusion prior to discharge (adjusted by baseline admission hematocrit).

v. Mean difference in hematocrit pre- & post-delivery (adjusted as for i.) above).

vi. Incidence of surgical treatment including uterine artery ligation or embolization, B-Lynch sutures or hysterectomy to control bleeding.

vii. Incidence of uterine tamponade to control bleeding.

viii. Incidence of Postpartum hemorrhage  $> 500$ cc determined clinically.

ix. Prolonged hospitalization ( $>2$ days).

x. Prevalence of endometritis.

xi. Hypotension requiring intravenous fluid bolus within one hour of delivery (adverse event).

xii. Incidence of presumed water intoxication (as defined in the hypotheses).

e. **Covariates:** All risk factors as above, gestational age stratification (<24, 24-31, 32-36, 37+ weeks) maternal age, parity, ethnicity, regional anesthesia, baseline hematocrit, causes of PPH other than atony (cervical, 2<sup>nd</sup> degree and 3<sup>rd</sup> or 4<sup>th</sup> degree lacerations), coagulopathy.

f. **Enrollment/Study Procedures (see Figure 1. for flow diagram):**

i.) Informed consent will be obtained by study personnel at the time of admission for vaginal delivery or soon after decision to deliver is made. Informed consent will be obtained for Spanish speaking women using interpreter. Women delivering precipitously, or unable to give consent will be excluded.

ii.) The pharmacy will procure or prepare the higher-dose and low-dose oxytocin infusions using the mechanism currently used for routine low dose standard. The pharmacy will sequentially number the higher or low dose oxytocin infusion following a confidential computer-generated random order (with code held by pharmacy). The infusions will be supplied weekly to a study-dedicated area on labor and delivery ensuring at least 70 are available weekly and dispensed for administration solely to enrolled patients following the assigned sequence. Usual (non-study) pitocin will also be readily available for those not included and will be dispensed following standard procedure. Nurses will carry study drugs to the operating room when vaginal delivery (e.g. of twins) is being performed. A quality control protocol will be developed by the pharmacy to ensure the randomization sequence is being followed and the right dose of oxytocin is being administered.

iii.) During the second stage of labor when vaginal delivery is anticipated, the nurse will take the next study infusion, pull off attached stickers with the sequential number and attach to the patients consent form, data collection form, and a research log. The patient will then be considered randomized into the study. Any remaining oxytocin bag used for labor induction or augmentation will be discarded at the time of delivery. If for any reason vaginal delivery does not occur, the study medication, if unused, will be routed back to the pharmacy for recycling into the randomization protocol.

g. **Sample size:**

*Primary hypothesis:* Considering 2-sided  $\alpha = 0.05$ ,  $P_0$  = Incidence (%) of women treated for uterine atony after standard low dose prophylactic pitocin, sample sizes assuming a 33% reduction ( $RR=0.67$ ) due to higher-dose 40U oxytocin for various estimates of  $P_0$  and specified power are presented in Table 4.

**Table 4. Sample size analyses for 3-arm oxytocin trial**

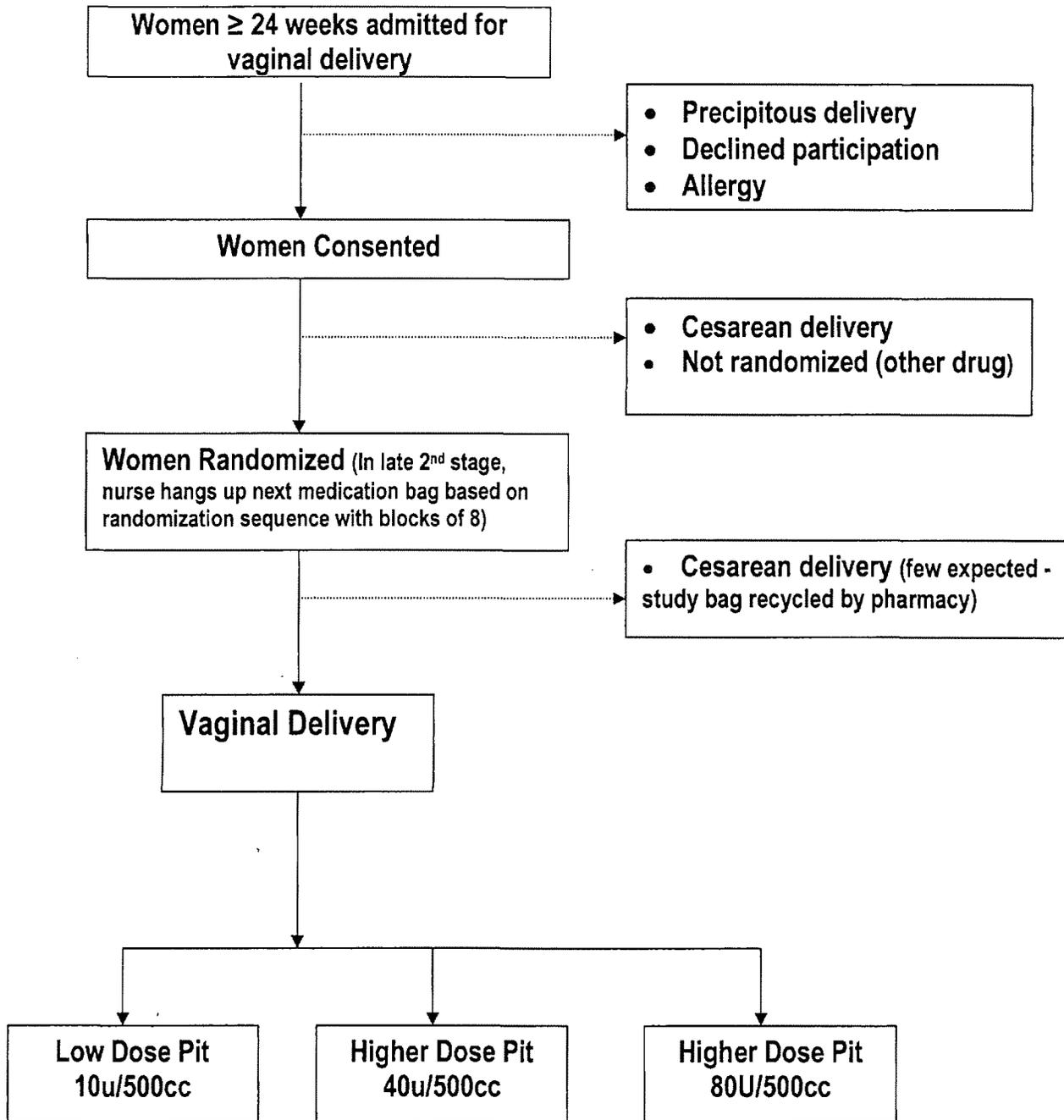
Power (%)	<u>Sample Size/Group (Total) assuming 33% reduction in treated atony</u>			
	$P_0=15\%$	$P_0=20\%$	$P_0=25\%$	$P_0=30\%$
80	<b>726 (1452)</b>	531 (1062)	404 (808)	313 (626)
90	957 (1914)	700 (1400)	532 (1064)	412 (824)

Similar computations assuming a 50% reduction ( $RR=0.5$ ) in treated atony due to higher-dose 80U relative to low dose pitocin yields sample sizes (80% power) of **304 (608)** if  $P_0=15\%$  and **220 (440)** if  $P_0=20\%$ .

A review of delivery logs and pharmacy records suggests  $P_0=15\%$ , corresponding to a sample size of about 1756 (726 in low-dose arm + 726 on higher-dose 40U + 304 on higher-dose 80U). If  $P_0$  is more frequent about 1500 or fewer total patients will be needed.

Furthermore regarding the 1<sup>st</sup> secondary hypothesis, our best estimate for  $P_0$  for high-risk women based on available literature and institutional review = 7-10%. A review deliveries at UAB for 2006 revealed that 50% of women are at highest risk for atony (Labor induction or augmentation > 6hours, Asian or Hispanic ethnicity, chorioamnionitis, intrapartum MgSO<sub>4</sub> use, birth weight  $\geq 4000$  g, twin pregnancy) and have a  $P_0$  (treatment other than oxytocic in this instance) of 10%, then the sample size determined above will provide 86% power to determine the postulated 60% reduction due to 40U pitocin and only 68% power for 50% reduction (recall in the cesarean study there was an 80% reduction in this outcome).

Figure 1: Flow Diagram for 3-arm Trial of Oxytocin to Prevent Obstetric Hemorrhage



Principal Investigator/Program Director (Last, First, Middle):

h. Data Collection and Analysis: Prepared data collection forms will be filled out with research data by trained research outcomes nurses and study investigators. Data entry, editing and analysis by departmental biostatistics staff.

i. Costs: It is anticipated that all patients will be charged for standard dose oxytocin (10 units/500cc) and this plan is approved by the IRB. Marginal costs for higher dose oxytocin (i.e. 30 additional units or 3 vials of 10 units for 726 patients and 70 additional units for 304 patients) will make up research costs (in addition to effort from research nurses and biostatistics staff). From speaking with the pharmacy supplier, marginal costs will be increased by about 18 dollars per 60 additional units or 3 dollars per 10 units. Thus, a ballpark cost for oxytocin (prior to any negotiations) is about \$ 13000.00 ( $726*3*3 + 304*7*3$ ). At the time of this submission a meeting has been scheduled with the Investigational Drug Pharmacists at \_\_\_\_\_ to plan to conduct of this trial.

j. Feasibility: Based on our current census at UAB (~ 3000 vaginal deliveries per year), we anticipate that this study will be completed and reported within the first 3 years of the k-23 award. See Table 7 for activity timelines for this study.

#### 4.2. Project 2: “Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) Study”

##### B.2. Specific aims:

Puerperal infection is a major cause of maternal morbidity and mortality in the US and elsewhere. Standard antibiotic prophylaxis, commonly a narrow-spectrum cephalosporin administered at cord clamp, led to important reductions in post-cesarean infectious morbidity. Despite routine prophylaxis infections still occur on average in 10% or more of cesareans. Given the rising rates of cesarean delivery, strategies to further reduce in infectious complications are sorely needed. We propose to evaluate 2 strategies to optimize the impact of antibiotic prophylaxis at cesarean section by modifying the spectrum and timing.

##### Primary Hypotheses:

- i.) Compared to narrow-spectrum cephalosporin alone, extended-spectrum prophylaxis (by adding azithromycin) will further reduce post-cesarean infection (endometritis or wound infection) by at least a third.
- ii.) Administration of prophylactic antibiotics prior to incision compared to at cord clamping will further reduce post-cesarean infection by at least a third.

##### Secondary Hypotheses:

- i.) Administration of prophylactic antibiotics prior to incision (compared to at cord clamping) will not be associated with an increase in the proportion of neonates with suspected sepsis who have negative septic workups.
- ii.) Administration of prophylactic antibiotics prior to incision (compared to at cord clamping) will not be associated with an increase in the proportion of neonates with proven sepsis with resistant organisms.
- iii.) Compared to narrow-spectrum cephalosporin alone, extended-spectrum prophylaxis will reduce post-cesarean fever and antibiotic therapy beyond 24hours post-delivery and maternal hospital stay.
- iv.) Administration of prophylactic antibiotics prior to incision compared to at cord clamping will reduce the post-cesarean fever and antibiotic therapy beyond 24hours post-delivery and maternal hospital stay.

##### B.2. Background and Significance

Puerperal infection, occurring within 42 days after delivery, remains a major cause of maternal mortality in the US and elsewhere [Berg, 2003]. Cesarean delivery is the most important risk factor for these postpartum infections, with over a 10 to 20-fold increase in risk for infectious morbidities such as endomyometritis, wound infection, pelvic abscess, septic pelvic phlebitis and sepsis compared to vaginal deliveries [Gibbs, 1980]. There is strong evidence that prophylactic antibiotics reduce the risk of post-cesarean fever and infectious morbidities by over 50% from baseline rates of 20-50% [Smaill, 2002]. This beneficial impact is definite for cesareans performed during labor, prolonged membrane rupture or for urgent indications. Systematic reviews also suggest an important benefit in elective (prelabor, non urgent) cesareans [Smaill, 2002; Chelmos, 2001]. ACOG therefore recommends prophylaxis for all women undergoing cesarean [ACOG Practice Bulletin, 2003].

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Narrow-spectrum prophylaxis with a 1<sup>st</sup> generation cephalosporin or Ampicillin is the regimen of choice. However, because of increasing resistance to Ampicillin, ACOG recommends use of a 1<sup>st</sup> generation cephalosporin. Antibiotic prophylaxis also reduces length of hospitalization and treatment costs and has been demonstrated to be a cost-effective strategy [Mugford, 1989; Chelmon, 2004].

The incidence of post-cesarean endometritis and wound infections vary widely by population profile such as socioeconomic status. Several other factors including the non-elective indications (labor, membrane rupture and fetal emergencies) increase the incidence [Gibbs, 1980]. Data from 39 trials conducted in the US out of 81 included in a Cochrane review indicated average incidences in post-cesarean endometritis of about 10-15 % and wound infection of 2-5% in the antibiotic arms [Smaill, 2002]. Data from about 40,000 cesareans at 13 US academic centers of the NICHD MFMU Network revealed rates of endometritis of 9% for non-elective and 4% for elective surgeries (overall incidence = 7%; range 2.2-13.3%) and a 1-2% wound infection rate [Goepfert, 2001]. It is noteworthy that these network figures are underestimates because follow-up was primarily only until hospital discharge from when a fair number of infections are not apparent. Taken together, the above suggest that despite antibiotic prophylaxis, over 10% of women undergoing non-elective, and over 5% of those undergoing elective cesarean suffer common infectious morbidity. Even higher proportions (over 15%) develop fever. These are certainly associated with prolonged antibiotic therapy and hospital stay and increased overall costs and probably with increased severe morbidity and maternal mortality. Given the ever rising rates of cesarean in the US - a 50% increase over the last decade to now involve a third of 4 million deliveries annually [Hamilton, 2007] - post-cesarean infection remains a public health priority in need of further remedial intervention(s). Two strategies appear promising:

#### i.) **Extended-Spectrum Antibiotic Prophylaxis**

Current recommendations are based on evidence indicating that prophylaxis with 1<sup>st</sup> generation cephalosporin (Cefazolin) or Ampicillin are as effective as broader spectrum antibiotics such as extended-penicillins and 2<sup>nd</sup> or 3<sup>rd</sup> generation cephalosporins [Hopkins, 2000]. Only 1 small trial out of 51 in a Cochrane review assessed the impact of the addition of a 2<sup>nd</sup> antibiotic other than a beta-lactam (Gentamycin) to ampicillin and reported a lower prevalence of endometritis (OR = 2.86; 1.1-7.8), febrile morbidity and longer hospitalization compared to ampicillin only [O'leary, 1986]. Increasing evidence indicates that when antibiotic spectrum is extended by adding a second antibiotic that does not belong to the beta-lactam class (e.g. azithromycin, gentamycin or metronidazole), there is an additional favorable impact on post-cesarean infections [O'leary, 1986; Pitt, 2001; Meyer, 2003]. The prospect that the addition of a 2<sup>nd</sup> antibiotic other than a beta-lactam may be associated with further reduction in post-cesarean infections is supported by the fact that post-cesarean infections are polymicrobial and the observation that antibiotic prophylaxis modifies maternal skin and genital flora towards increased presence of resistant organisms such as anaerobes. Furthermore, Ureaplasma and bacterial vaginosis, which are not covered by standard antibiotic prophylaxis, have been associated with increased risk of post-cesarean infection [Rosene, 1986; Watts, 1990; Roberts, 1993; Keski-Nisula, 1997; Yoon, 1998]. In fact, these data and others suggest that when sought, Ureaplasma is the most common isolate from endometritis or wound infections.

The addition of Azithromycin (presumably to cover for ureaplasma) to standard cephalosporin prophylaxis has been demonstrated in one clinical trial to further reduce post-cesarean endometritis (by a third), wound infection and hospital stay. Because intravenous Azithromycin was not available during the trial, intravenous doxycycline after cord clamping and oral azithromycin 6-12 hours later was used. Subsequently, we have demonstrated a remarkable biphasic drop in post-cesarean endometritis from >20% to 4% coincident with the clinical trial and a new policy of routine extended prophylaxis with the addition of intravenous Azithromycin at cord clamp compared to the period prior to this extension [ ]. In an abstract presented at the SMFM this year, we also demonstrate a decreasing incidence of wound infections over the same 3 time periods. [ ] This practice of routine extended-spectrum prophylaxis is unique : among the 14 centers of the MFMU Network and likely represents the situation across the country. Therefore, a large multi-center study involving patients with diverse demographic characteristics is needed to confirm the previous findings and the generalizability to other settings. Azithromycin has a long half-life, high tissue concentration, reduced fetal transfer, suggested impact on both wound infection and endometritis and aerobic and some anaerobic coverage (and certainly covers for Ureaplasma) and thus appears to be an excellent candidate to extend antibiotic spectrum.

**ii.) Timing of Prophylaxis before incision (vs. after cord clamping)**

Because of observations that antenatally-administered beta-lactams rapidly cross to the fetal compartment and concerns that this might adversely affect the neonate by masking infection and/or select resistant organisms, antibiotics are most commonly administered after cord clamping [Smail, 2002; ACOG Practice Bulletin, 2003]. This practice is supported by early research studies that indicated no maternal benefit from administration prior to incision [Gordon, 1979; Cunningham, 1983] in addition to possible neonatal harm and increased costs from excess neonatal sepsis workups due to concern from pediatricians about masked infection as a result of antibiotic exposure [Cunningham, 1983]. Although ACOG does not give an explicit recommendation regarding timing, it recognizes that prophylactic antibiotics for cesarean are most commonly administered at cord clamp [ACOG Practice Bulletin # 47, 2003]. The CDC explicitly recommends prophylaxis after cord clamp [Mangram, 1999]. Although non-obstetric animal and human studies suggest that administration of antibiotic prophylaxis prior to incision is more effective [Classen, 1992], studies of cesarean prophylaxis remain inconclusive regarding the superiority of administration prior to incision [Gordon, 1979; Cunningham, 1983; Wax, 1997; Thigpen, 2005; Sullivan, 2007]. The most recent trial by Sullivan, with patients from a single center (N=357) and probably the best designed to date on this issue, revealed a significant reduction in endometritis and combined infectious morbidity (including urinary infections). However, at the time of this submission, I have been asked to review another trial involving over 500 patients, which suggests no advantage to administration prior to incision. As of 7/07 only 3-4 out of 14 MFMU network centers surveyed administered prophylaxis prior to incision [7]. Therefore another large trial is needed to definitively address this issue of timing.

A factorial trial is the most efficient design to address both these questions of extended prophylaxis and timing of prophylaxis [Brittain, 1989; Montgomery, 2003; McAlister, 2003]. Timing and spectrum are independent concepts and our primary interest is their main effects (the trial is therefore powered for main effects). An interaction between timing and spectrum will be sought as a secondary outcome. Even if present it is highly unlikely to be a negative interaction, therefore our power to assess the main effects will not be impaired.

**B.3 Preliminary Studies/Progress Report:**

As detailed above Dr. [redacted] or his mentors at [redacted] conducted some of the previous studies on antibiotic prophylaxis (the pertinent studies are highlighted in bold font above). Dr. [redacted] also surveyed the centers of the MFMU network to determine their current practices regarding timing and antibiotic regimens. This factorial trial concept has been presented by [redacted] to the MFMU Network Steering Committee and has been overwhelmingly approved as a concept for study. With the mentorship [redacted] and [redacted] both the PI and Alternate PI for [redacted] network site, [redacted] will work over the first 1-2 years of the career development award to prepare a mini-protocol and subsequently a full protocol for discussion, input and approval at the network steering committee which involves all PI. The research methods for this study are briefly outlined below.

**B.4. Research Design and Methods Overview**

A 2x2 factorial (spectrum and timing) multi-center randomized placebo-controlled clinical trial will be conducted.

- a. Setting: NICHD MFMU Network centers
- b. Inclusion Criteria: Women  $\geq$  24 weeks undergoing non-elective and elective cesarean.
- c. Exclusion Criteria: Allergies to study antibiotics or lack of consent.
- d. Primary Outcomes: Incidence of endometritis or wound infection (within 2-6 weeks of delivery).
- e. Secondary Outcomes:
  - i. Prevalence of negative neonatal septic work-ups.
  - ii. Prevalence of sepsis with resistant organisms.
  - iii. Prevalence of each of febrile morbidity, endometritis, wound infection, maternal hospital stay >4days, neonatal hospital stay>4 days, serious maternal morbidity or death.
  - iv. Interaction between spectrum and timing of prophylaxis for primary outcome (\*required for all factorials).
  - v. Adverse reactions.

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f. **Interventions:** Factorial administration of antibiotics in four possible active combinations stratified by center (Table 5). For each of these active arms double blinding will be achieved by administering 2 placebo bags before or after as appropriate.

**Table 5: Factorial design: Active arms**

	<i>Extended-spectrum</i>	<i>Control</i>
<i>Before incision</i>	Cefazolin + Azithromycin (n=a)	Cefazolin + Placebo (n=b)
<i>At cord clamp</i>	Cefazolin + Azithromycin (n=c)	Cefazolin + placebo (n=d)

Intravenous antibiotic doses: Cefazolin 1-2g and Azithromycin 500mg

g. **Alternative Designs and Sample Size:** Estimated sizes assuming no interactions, 80% power and 2-sided alpha for 7.5% or 10% or 12% baseline incidences of endometritis or wound infection with cefazolin only given at cord clamp, and for minimum effect sizes (reductions) of 25% or 33% are given for alternative designs (Table 6):

**Table 6: Sample size analyses for factorial trial and alternative designs**

Baseline incidence of endometritis or wound infection	Minimum effect size (% reduction)	
	25%	33%
<b>7.5%</b>		
Factorial design	5530	3100
Two separate trials	11060	6200
Single 3 arm trial*	8295	4650
<b>10%</b>		
Factorial design	4168	2324
Two separate trials	8336	4648
Single 3 arm trial*	6252	3486
<b>12%</b>		
Factorial design	3408	1864
Two separate trials	6816	3728
Single 3-arm trial*	5112	2796

\*Cefazolin + Azithromycin at cord clamp or Cefazolin only prior to incision vs. Cefazolin only at cord clamp

**\*\*The factorial design is the most efficient for all scenarios in the table. In addition, it is the only one that allows for assessing possible interaction. The anticipated conservative sample size = 3100.**

h. **Feasibility:** Considering that about 35,000 cesareans are performed annually at the current 14 MFMU network centers, the study can therefore be completed within 1-2 years of initiating enrollment. This is anticipated to correspond to years 3-4 of the career development award.

i. **Implementation:** The study will be planned in conjunction with the NICHD MFMU Network Biostatistical Coordinating Center and in consultation with the steering committee (see Table 7 for activity timeline).

j. **Funding:** Studies conducted within the MFMU-Network are funded by the NICHD

k. **Contingency plans:** It is possible that the waiting period for prioritization of this study may be longer than expected because of delays in ongoing studies or competition from other approved studies. For several reasons we believe this scenario is unlikely: there is no other approved study focusing on cesareans (most of the other studies focus on preterm birth and would compete more with each other), the study will be relatively

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inexpensive because of the one time intervention, the short follow-up duration and because antibiotic prophylaxis is standard of care (and therefore the study can cover only the marginal costs of extending the spectrum and providing placebo). In addition, while awaiting prioritization, the MFMU Network process allows us the option to seek for outside funding from other interested agencies (such as the CDC or Private agencies) which may accelerate prioritization. The recently completed BEAM study (Magnesium sulfate and cerebral palsy) of the NICHD MFMU Network ( as Principal Investigator) received such an impetus from the National Institute of Neurological Disorders and Stroke (NINDS). We therefore plan to seek additional funding while awaiting prioritization. This will enrich Dr. experience through the grant-writing and networking efforts involved.

**N.B. The sections that follow apply to both proposed research projects.**

**Table 7: Timeline of practical research activities during the award period**

<b>Award Year</b>	<b>Project 1: 3-arm Oxytocin Trial</b>	<b>Project 2: C/SOAP Factorial Trial (MFMU Network)</b>	<b>Other Research Projects</b>
<b>Year 1</b>	Complete planning Begin patient enrollment	Develop study protocol	Database analyses (continuous) In-depth review (antibiotic - microbial interactions)
<b>Year 2</b>	Continue patient enrollment	Complete study protocol Await protocol prioritization	Metaanalysis (Extended prophylaxis) Design pilot (interactions) Planning cluster RCT
<b>Year 3</b>	Complete enrollment Data analysis Communicate results	Protocol prioritized Pilot of study protocol Begin patient enrollment	Ongoing grant applications Database analyses (continuous) Pilot studies (interactions)
<b>Year 4</b>	N/A	Continue patient enrollment	Database analyses (continuous) Planning/initiation of cluster RCT Cost effectiveness analysis (oxytocin protocols)
<b>Year 5</b>	N/A	Complete patient enrollment Data analysis Begin to communicate results	Ongoing grant applications Cost effectiveness analyses (antibiotic prophylaxis protocols)

**E. Human Subjects research**

This Human Subjects Research projects meet the definition of a clinical trial. Project 1 is already IRB approved at our center.

**1) Protection of Human Subjects**

**E.1.1 Risks to Human Subjects:**

For Project 1, pregnant women will be randomized to 3 arms of oxytocin to be administered immediately after vaginal delivery. A total of about 1500-2000 women will be enrolled. Based on the profile of our center's delivery population we anticipate the demographic breakdown will be 60% African American, 30% Caucasian and 10% Hispanic. Apart from medical contraindications to oxytocin, no specific subgroup will be excluded. Obviously, only pregnant women will be included as this study is relevant to them only. Maternal demographic and clinical data will be obtained. The research outcomes nurse and the PI will collect outcome data. The statistician and research analyst will be responsible for data entry and preparation of a deidentified dataset.

For Project 2, pregnant women undergoing cesarean section will be randomized to arms of the factorial interventions. A total of 3100 women will be enrolled. Based on the profile of women delivered within the MFMU Network we anticipate the following demographic breakdown: 50% Caucasian, 25% Hispanic, 20% African American and 5% Asian or other. Again only pregnant women will be included. Maternal and neonatal demographic and clinical information will be collected by research outcomes nurses and conveyed to the Data coordinating center of the MFMU Network. The Network has strict and tested rules for protecting private information.

Principal Investigator/Program Director (Last, First, Middle):

The potential risks to subjects from both studies are minimal – the interventions in both projects involve a modification of standard treatments. High dose of oxytocin has been previously used in a clinical trial without any adverse events noted.

*E.1.2 Adequacy of Protection against risks*

Written informed consent will be obtained by study nurses and physicians on labor and delivery for both projects. The informed consent forms will, in plain language, explain the study purpose and plan and the contact information of the PI provided.

All study subjects will be closely monitored on labor and delivery, the recovery area and on the postpartum floor. Any suspected adverse effects will be dealt with immediately by an on-call (24 hours a day) physician. Confidentiality will be maintained by assigning each patient a unique study number. Adverse event monitoring will be conducted and reported to a constituted Data Safety and Monitoring Board empowered to stop the trial if necessary.

*E.1.3 Potential benefits of the proposed research to human subjects*

The research projects are likely to lead to improved prevention of obstetric hemorrhage and post-cesarean infection, both major causes of maternal morbidity and mortality. The anticipated benefits outweigh any minimal risks from the interventions.

*E.1.4 Importance of the knowledge to be gained*

As indicated above, the knowledge gained may lead to prevention of maternal morbidity and possibly mortality from 2 major causes.

*E.1.5 Data and safety monitoring plan*

For Project 1, a DSMB will be constituted at our center, comprising staff members who are not otherwise involved with the study. Weekly adverse event reporting will be the responsibility of the PI. The DSMB will determine the necessity to un-blind or terminate the trial.

For Project 2, a DSMB will be constituted following established MFMU Network rules.

*E.1.6 Clinical trials.gov Requirements:*

This application includes 2 clinical trials, which will be registered at clinical trials.gov. prior to the starting enrollment.

**2) Inclusion of Women and Minorities:** Both trials will include consenting pregnant women of all ethnicities and age groups. Men are excluded because the study question does not apply to them.

**3) Inclusion of children:** Both studies proposed target pregnant women without age restriction. Obviously, the vast majority is expected to be older than 18 years but those younger will be also be enrolled if consent is provided.

**4) Targeted/Planned Enrollment Table:** Anticipated enrollment tables for both projects are provided below.

## Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

**Study Title:** Higher vs. Lose-dose Oxytocin to Prevent Uterine Atony and Hemorrhage at Vaginal Delivery

**Total Planned Enrollment:** 1750

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	175		175
Not Hispanic or Latino	1,575		1,575
<b>Ethnic Category: Total of All Subjects *</b>	1,750		1,750
Racial Categories			
American Indian/Alaska Native	10		10
Asian	30		30
Native Hawaiian or Other Pacific Islander	10		10
Black or African American	1,050		1,050
White	650		650
<b>Racial Categories: Total of All Subjects *</b>	1,750		1,750

\* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

Principal Investigator/Program Director (Last, First, Middle):

## Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) Study

Total Planned Enrollment: 3100

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	775		775
Not Hispanic or Latino	2,325		2,325
<b>Ethnic Category: Total of All Subjects *</b>	<b>3,100</b>		<b>3,100</b>
<b>Racial Categories</b>			
American Indian/Alaska Native	20		20
Asian	120		120
Native Hawaiian or Other Pacific Islander	15		15
Black or African American	630		630
White	2,315		2,315
<b>Racial Categories: Total of All Subjects *</b>	<b>3,100</b>		<b>3,100</b>

\* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

F. Vertebrate Animals: Not applicable

G. Select Agent Research: Not applicable

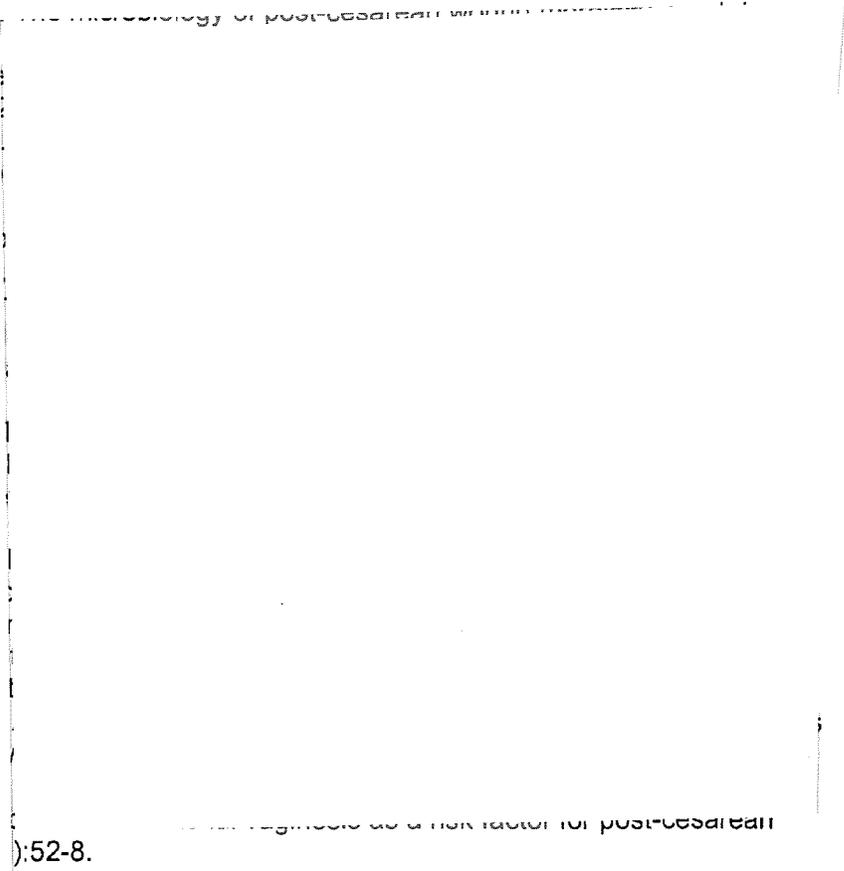
H. Literature Cited (Research Plan Only)

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**I. Consortium/Contractual Agreements:** Not applicable to the funding mechanism for this career development award (although the 2<sup>nd</sup> project will be performed within the MFMU Network)

**J. Resource Sharing Plans:** Not applicable to the funding mechanism for this career development award (although the 2<sup>nd</sup> project will be performed within the MFMU Network)

**CHECKLIST**

**TYPE OF APPLICATION** (Check all that apply.)

- NEW application. (This application is being submitted to the PHS for the first time.)
- REVISION/RESUBMISSION of application number: \_\_\_\_\_  
(This application replaces a prior unfunded version of a new, competing continuation/renewal, or supplemental/revision application.)
- COMPETING CONTINUATION of grant number: \_\_\_\_\_  
(This application is to extend a funded grant beyond its current project period.)
- SUPPLEMENT/REVISION 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: \_\_\_\_\_
- CHANGE of Grantee Institution. Name of former institution: \_\_\_\_\_
- FOREIGN application or significant foreign component.  Domestic Grant with foreign involvement. List Country (ies) Involved: \_\_\_\_\_

**1. PROGRAM INCOME** (See instructions.)

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
N/A	N/A	N/A

**2. ASSURANCES/CERTIFICATIONS** (See instructions.)

In signing the application Face Page, the authorized organizational representative agrees to comply with the following policies, assurances and/or certifications when applicable. Descriptions of individual assurances/certifications are provided in Part III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

- Human Subjects; •Research Using Human Embryonic Stem Cells•
- Research on Transplantation of Human Fetal Tissue •Women and Minority Inclusion Policy •Inclusion of Children Policy• Vertebrate Animals•

- Debarment and Suspension; •Drug- Free Workplace (applicable to new [Type 1] or revised/resubmission [Type 1] applications only); •Lobbying;
- Non-Delinquency on 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); •Recombinant DNA Research, Including Human Gene Transfer Research; •Financial Conflict of Interest •Smoke Free Workplace; • Prohibited Research; • Select Agent Research • PI Assurance

**3. FACILITIES AND ADMINISTRATION COSTS (F&A)/INDIRECT COSTS.** See specific instructions.

- DHHS Agreement dated: 06/29/06  No Facilities And Administrative 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: \$ <u>119,763</u> x Rate applied <u>8.00</u>	% = F&A costs \$ <u>9,581</u>
b. 02 Year	Amount of base: \$ <u>122,326</u> x Rate applied <u>8.00</u>	% = F&A costs \$ <u>9,786</u>
c. 03 Year	Amount of base: \$ <u>120,509</u> x Rate applied <u>8.00</u>	% = F&A costs \$ <u>9,641</u>
d. 04 Year	Amount of base: \$ <u>123,080</u> x Rate applied <u>8.00</u>	% = F&A costs \$ <u>9,846</u>
e. 05 Year	Amount of base: \$ <u>119,446</u> x Rate applied <u>8.00</u>	% = F&A costs \$ <u>9,556</u>
TOTAL F&A Costs \$		<b>48,410</b>

\*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.):

SCHOOL OF  
MEDICINE

*Department of Obstetrics and Gynecology*

February 05, 2008

FEB 14 2008

Center for Scientific Review  
National Institutes of Health  
Bethesda, Maryland

RE:

To Whom It May Concern:

This letter provides strong support of \_\_\_\_\_ a candidate for a K-23 career development award. I have known \_\_\_\_\_ since he applied for fellowship training in Maternal-fetal Medicine at the University of \_\_\_\_\_ currently our most senior fellow, he began our 3-year program in 2005 and is expected to finish in June, 2008. Prior to fellowship training, Dr. \_\_\_\_\_ completed a concurrent doctoral degree curriculum in Public Health and a 4-year residency in Obstetrics and Gynecology in \_\_\_\_\_. As the MFM fellowship program director for the past 13 years I can attest that no fellow has accomplished as much as Dr. \_\_\_\_\_ who continues to exhibit the rare combination of clinical prowess, research aptitude, educational skills and goal-oriented energies. As his vitae confirm, he has demonstrated indefatigable drive to design, conduct and publish clinical research under the mentorship of senior academic faculty in our division. While many of Dr. \_\_\_\_\_ professional skills have been enlarged during fellowship, his training is incomplete.

This career development award will ensure that Dr. \_\_\_\_\_ can mature into an independent, funded clinical investigator by providing the resources and protected time to develop and conduct large-scale clinical trials under, for example, the auspices of the NICHD MFM Units Network, of which \_\_\_\_\_ has been an active clinical center since 1990. His concept, a randomized trial of extended spectrum antibiotic prophylaxis and timing of administration for the prevention of post-caesarean surgical infections, will be advancing into protocol form and will likely change practice on an international scale. Notably, it utilizes an efficient factorial design which represents the first time in the history of the Network that such a trial design was approved and with enthusiasm. This trial also effectively synthesizes both unique microbiological concepts and previous scientific literature spanning several disciplines.

Our division is fortunate to have on staff, 3 past and present Network Primary Investigators whose collective experience in clinical trial design, funding and publication, is unparalleled and at Dr. \_\_\_\_\_ educational disposal. Also at \_\_\_\_\_'s disposal are associated department

researchers who have successfully competed for extramural funding from a variety of sources and may serve as academic role models and collaborators. A research infrastructure staffed with specialists in budget development, biostatistics, nursing coordination and investigational review boards is also on site. This interactive exposure, of course, is crucial to Dr. [redacted] uninterrupted progress and continuing success in academic medicine.

On a more personal note, [redacted]'s commitment to health-oriented research has received international attention from his recent cover-feature article (7) published in Obstetrics and Gynecology, lamenting the failure of international health initiatives to improve perinatal care delivery in underdeveloped areas, such as his home country of [redacted] and colleagues critically examine the pathways to failure and promote new research designs and implementation strategies to identify effective interventions and translate them into clinical practice. In his position as a clinical fellow, Dr [redacted] has also devoted his energy toward mentoring several of our Obstetric and Gynecologic residents in their obstetric research initiatives, so perpetuating academic development.

Although his fellowship has been extraordinarily productive and has provided Dr [redacted] with both an excellent clinical skill set and an introduction into a career of productive clinical investigation, [redacted] clearly has the motivation and aptitude to take maximum advantage of our department's varied resources and complete high-level career development. We believe that as a recipient of this competitive award, [redacted] will develop into a clinical scientist with international recognition and further serve the clinical and academic communities by the assumption of productive and important roles in Women's health care.

Sincerely,

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## CAREER DEVELOPMENT AWARD REFERENCE REPORT GUIDELINES

Title of Award: Career Development <sup>(Series K)</sup> Award in Obstetric & Perinatal Research

Type of Award: K23

FEB 14 2008

Application Submission Deadline: 2/12/08

Name of Candidate (Last, first, middle):

Name of Respondent (Last, first, middle):

The candidate is applying to the National Institutes of Health for a Career Development Award (CDA). The purpose of this award is to develop the research capabilities and career of the applicant. These awards provide up to five years of salary support and guarantee them the ability to devote at least 75 percent of their time to research for the duration of the award, depending on the specific program for which the candidate is applying. Many of these awards also provide funds for research and career development costs. The award is available to persons who have demonstrated considerable potential to become independent researchers, but who need additional supervised research experience in a productive scientific setting.

We would appreciate receiving your evaluation of the above candidate with special reference to:

- potential for conducting research;
- evidence of originality;
- adequacy of scientific background;
- quality of research endeavors or publications to date, if any;
- commitment to health-oriented research; and
- need for further research experience and training.

Any related comments that you may wish to provide would be welcomed. These references will be used by PHS committees of consultants in assessing candidates.

Complete the report in English on 8-1/2 x 11" sheets of paper. Return your reference report to the candidate sealed in the envelope as soon as possible and in sufficient time so that the candidate can meet the application submission deadline. References must be submitted with the application.

We have asked the candidate to provide you with a self-addressed envelope with the following words in the front bottom corner: "DO NOT OPEN—PHS USE ONLY." Candidates are not to open the references. Under the Privacy Act of 1974, CDA candidates may request personal information contained in their records, including this reference. Thank you for your assistance.

FEB 14 2008

February 7, 2008

RE: PH, PhD

Review Committee Member:

has proven to be adept at conceptualizing, accomplishing, and publishing original research. His well planned career path reflects a long standing commitment to women's reproductive health research at the highest academic levels in the United States. His MD was obtained at the University of followed by an MPH in International Health at the University of in the . He began a postgraduate program in Epidemiology at the University of h in 1999 and obtained his PhD (with a minor in biostatistics) in 2004 while completing his Obstetrics and Gynecology residency at College of Medicine. He will complete our Maternal-Fetal Medicine fellowship at on June 30, 2008.

's academic research potential is immense. He has 21 original peer reviewed publications, 16 as first author. A 2007 *American Journal of Obstetrics and Gynecology* manuscript was an "editor's choice." He has had two oral and multiple poster presentations (2006-2007) at the prestigious annual meeting of the Society for Maternal-Fetal Medicine. His research proposal, at the January 2008 NICHD Maternal-Fetal Medicine Units Network Steering Committee, was approved to proceed to full protocol and implementation.

In summary, has an appreciable and outstanding career development and scientific background and immense potential for conducting research. To date, he has been very productive in original and high quality research and publications. s career development plan and accomplishments clearly attest to his commitment to women's reproductive health oriented research.

has not had experience in developing and accomplishing large, randomized, double-blinded clinical trials at either one or multicenter collaborations. This is of importance since Dr. long term goals not only include continuing his epidemiologic and clinical research as encompassed within his curriculum vitae but also to develop and complete large randomized and multicenter clinical trials to address major clinical care issues within the United States and in selected international areas. Thus the importance of Dr. K23 application, which primarily is focused on the expansion of knowledge and experience in this major area of his research interests. The development and operational complexities of conducting large multicenter and international trials are immense. Our department and Dr. primary mentors (Drs. ) have extensive expertise and experience in all of

RE: \_\_\_\_\_, MD, MPH, PhD  
February 7, 2008  
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these areas and issues. \_\_\_\_\_'s mentors have devoted immense time assisting Dr. \_\_\_\_\_ in the near final development of the two trials Dr. \_\_\_\_\_ has included in his research plans. Data forms, budgets, double-blinded medications, randomization schemes have all been studied, developed and the trials are nearly final prior to implementation. I am confident that Dr. \_\_\_\_\_ will have a continued commitment to and outstanding success within women's reproductive health-oriented research.

I strongly endorse Dr. \_\_\_\_\_ K23 application and encourage your consideration of his proposals.

Sincerely,

**Department of Obstetrics and Gynecology**

February 4, 2008

Center for Scientific Review  
National Institute of Health  
Bethesda, MD

Dear Reviewer:

This is a recommendation for [redacted] for the NIH Career Development Award. I have had the very great pleasure of working with [redacted] since he came to work at the Department of OBGYN at University of [redacted] as a fellow in Maternal Fetal Medicine nearly three years ago. During that time, I have served as a collaborator and mentor on a number of his projects and continue to do so despite my moving to [redacted] one year ago. I expect this relationship will continue, especially because of our common interest in global health and infection-related pregnancy outcomes.

This recommendation is very easy to write because [redacted] is among the most talented, thoughtful and hardest working fellows/young scientists with whom I have ever worked. He always brings new ideas to the table, is never at a loss for new and interesting projects, and thinks big in that he wants to study and solve important questions. Overall, I think he has the potential to be an important leader in the field of pregnancy outcome research for years to come. As an example, at this year's Society of Maternal Fetal Medicine meeting, [redacted] presented data on iatrogenic neonatal disease associated with too early elective cesarean section, showing significant morbidity associated with this practice. I thought that this was the most important presentation at the meeting and certainly the one with the greatest potential to change practice. Representatives of The American College of OBGYN have already stated that they will use his data as part of their teaching programs. By the way, having an oral presentation at this meeting is an honor in itself since only 80 of 1600 abstracts submitted are chosen for oral presentation. This is the second year in a row that [redacted] has achieved such an honor. His presentations are clear, concise and very well received.

RE:

's interest in global health substantially increases his potential value as a research scientist. Coming originally from he clearly has an interest in participating in and originating studies to improve pregnancy outcomes in developing countries as well as the US. His editorial on maternal mortality published recently in the journal *Obstetrics and Gynecology* was important and well-received by the obstetric community. In designing a large multi-country cluster randomized study to reduce stillbirth and neonatal mortality, I consulted extensively on the interventions, and he will be a collaborator on this project. This commitment to global maternal and perinatal health makes an even more attractive candidate for this award.

already has substantial training in epidemiology and data analysis using existing data sets. In this proposal, is seeking support to extend his expertise to the conduct of large-scale clinical trials. The two trials he is proposing (a 3-arm trial of prophylactic oxytocin for uterine atony among vaginal births and a factorial design trial of extended spectrum vs. standard prophylaxis and timing before incision vs. after cord clamping to prevent post-cesarean endometritis or wound infection) will answer important research questions, are feasible to carry out within available resources, and will provide with the experience he needs to become an independent investigator. When his proposed training plan is completed, and the proposed trials are finished, he should have all the expertise and experience necessary to ensure that he will become an independent investigator, and one capable of attaining significant independent grant support to carry out his research.

In summary, has tremendous potential to benefit from this award and with it will become one of the leaders in pregnancy outcomes research. You will be proud to have him as a Career Development Award alumnus. If I can provide additional information please let me know.

Sincerely

enclosure