Grant Number: 1R03NR012558-01 REVISED

Principal Investigator(s):
AARON M MILSTONE, MD

Project Title: Catheter Dwell Time and Risk of Bloodstream Infections in Hospitalized Neonates

Pio Roda, Marissa
Grants Associate
733 North Broadway, BRB 117
733 North Broadway, BRB 117
Baltimore, MD 21287

Award e-mailed to: NIH@RESOURCE.CA.JHU.EDU

Budget Period: 09/30/2010 – 07/31/2011
Project Period: 09/30/2010 – 07/31/2012

Dear Business Official:

The National Institutes of Health hereby revises this award (see “Award Calculation” in Section I and “Terms and Conditions” in Section III) to JOHNS HOPKINS UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the “Terms and Conditions” is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release or other document that cites results from NIH grant-supported research must include an acknowledgment of NIH grant support and disclaimer such as “The project described was supported by Award Number R03NR012558 from the National Institute Of Nursing Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of Nursing Research or the National Institutes of Health.”

Award recipients are required to comply with the NIH Public Access Policy. This includes submission to PubMed Central (PMC), upon acceptance for publication, an electronic version of a final peer-reviewed, manuscript resulting from research supported in whole or in part, with direct costs from National Institutes of Health. The author’s final peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. For additional information, please visit http://publicaccess.nih.gov.

Award recipients must promote objectivity in research by establishing standards to ensure that the design, conduct and reporting of research funded under NIH-funded awards are not biased by a conflicting financial interest of an Investigator. Investigator is defined as the Principal Investigator and any other person who is responsible for the design, conduct, or reporting of NIH-funded research or proposed research, including the Investigator's spouse and dependent children. Awardees must have a written administrative process to identify and manage financial conflict of interest and must inform investigators of the conflict of interest policy and of the Investigators' responsibilities. Prior to expenditure of these awarded funds, the Awardee must report to the NIH Awarding Component the existence of a conflicting interest and within 60 days of any new conflicting interests identified after the initial report. Awardees must comply with these and all other aspects of 42 CFR Part 50, Subpart F. These requirements also apply to subgrantees, contractors, or collaborators engaged by the Awardee under this award. The NIH website http://grants.nih.gov/grants/policy/coi/index.htm provides additional information.
If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Kelli Oster
Grants Management Officer
NATIONAL INSTITUTE OF NURSING RESEARCH

Additional information follows
SECTION I – AWARD DATA – 1R03NR012558-01 REVISED

Award Calculation (U.S. Dollars)

Federal Direct Costs $68,293
Federal F&A Costs $43,707
Approved Budget $112,000
Federal Share $112,000
TOTAL FEDERAL AWARD AMOUNT $112,000

AMOUNT OF THIS ACTION (FEDERAL SHARE) $0

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Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project.

Fiscal Information:
CFDA Number: 93.361
EIN: 
Document Number: RNR012558A
Fiscal Year: 2010

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Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project.

NIH Administrative Data:
PCC: CIFXT / OC: 414A / Processed: OSTERK 10/25/2010

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R03NR012558-01 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R03NR012558-01 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at 'http://grants.nih.gov/grants/policy/awardconditions.htm' for certain references cited above.)

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase V Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.
Treatment of Program Income:
Additional Costs

SECTION IV – NR Special Terms and Conditions – 1R03NR012558-01 REVISED

INFORMATION: RESCIND HUMAN SUBJECTS RESTRICTION
This revised award removes the provisional term from the award issued on 9/30/10 and reflects NINR's receipt and acceptance of the certification of IRB approval 10/4/10.

INFORMATION: RESCIND HUMAN SUBJECTS & OTHER SUPPORT RESTRICTION
This revised award removes the provisional term on the award issued on 9/30/10 and reflects the NINR's receipt and acceptance of the required Human Subjects Education Certification and other support for key personnel.

INFORMATION: This award provides partial funding in the amount of $112,000 total costs for the -01 year. NINR intends to restore funding to the full funding level of $116,196 total costs ($70,851 direct costs and $45,345 associated F&A costs) in Fiscal Year 2011 if funds are available.

INFORMATION: No salary support for Dr. Milstone may be charged to this grant during his support under K23 AI81752-01.

INFORMATION: KEY PERSONNEL
The grantee's 9/28/10 request to reduce the PI's effort to .6 CM has not been approved. Any absence, replacement, or substantial reduction in effort of Dr. Aaron Milstone, PI (1.2 CM) requires the written prior approval of the National Institutes of Nursing Research.

INFORMATION: MODULAR GRANT AWARD
This is a modular grant award without direct cost categorical breakdown in accordance with the guidelines published in the NIH Grants Policy Statement (revised December 2003) (see http://grants1.nih.gov/grants/policy/nihgps_2003/nihgps_2003.pdf). Recipients are required to allocate and account for costs related to this award by category within their institutional accounting system in accordance with applicable cost principles.

INFORMATION: NINR ADJUSTMENTS FOR SALARY BASED AWARDS:
Salary funds provided on NINR research grants will be adjusted if investigators receive career-type salary based awards. In the event that such an award is made for an investigator receiving salary support from an NINR grant, the National Institute of Nursing Research must be informed in writing within 30 days from the start date of the award so that any required adjustment can be made.

INFORMATION: HUMAN SUBJECTS EDUCATION CERTIFICATION
This award reflects the National Institute of Nursing Research acceptance of the certification that all key personnel as defined in the February 29, 2008 NIH Guide announcement (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html) have completed education on the protection of human subjects, in accordance with NIH policy requirements. Any key personnel, as defined in that announcement, who are not included in the list dated 9/27/10 as of 10/1/10, must satisfy this requirement prior to participating in the project. Failure to comply can result in suspension and/or termination of this award or withholding of support of the continuation award.

INFORMATION: BUDGET/PROJECT PERIOD ADJUSTMENT
This grant has been selected under the NINR plan to redistribute grant workloads more evenly throughout the year. Consequently, the initial budget period reflects a 7/31/11 end date. Subsequent budget periods will begin on August 1 and will be for twelve months. Although this grant will have a slightly shorter budget period this year, it is awarded a full twelve months of funds for the budget period. Additional time may be requested at the end of the project period if needed.

INFORMATION: CONSORTIUM/CONTRACTUAL COSTS
This award includes funds for consortium activity with the following organizations:
Children's Hospital of Philadelphia
Children's Mercy Hospital
Columbia University
Duke University
George Washington University
Mayo Clinic
University of Louisville
Each consortium is to be established and administered in accordance with the NIH Grants Policy
Statement dated December 2003. No foreign performance site may be added to this project
without the written prior approval of the National Institute of Nursing Research.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of
this project and for interpretation of Grants Administration policies and provisions. The Program
Official is responsible for the scientific, programmatic and technical aspects of this project. These
individuals work together in overall project administration. Prior approval requests (signed by an
Authorized Organizational Representative) should be submitted in writing to the Grants
Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Kelli Oster
Email: osterk@mail.nih.gov Phone: 301.594.2177

Program Official: Joan Wasserman
Email: wassermanje@mail.nih.gov Phone: 301-594-5971 Fax: 301-480-8260

SPREADSHEET SUMMARY
GRANT NUMBER: 1R03NR012558-01 REVISED

INSTITUTION: JOHNS HOPKINS UNIVERSITY

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**PI: MILSTONE, AARON M**
Title: Catheter Dwell Time and Risk of Bloodstream Infections in Hospitalized Neonates

Received: 02/19/2010  FOA: PA10-064  Council: 10/2010
Competition ID: ADOBE-FORMS-B  FOA Title: NIH Small Research Grant Program (Parent R03)
**1 R03 NR012558-01**  Dual: AI,HD  Accession Number: 3274200
IPF: 4134401  Organization: JOHNS HOPKINS UNIVERSITY
Former Number:  Department: PEDIATRIC INFECTIOUS DISEASES

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**Senior/Key Personnel:**

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<tr>
<td>Aaron Milestone</td>
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<tr>
<td>Kristina Bryant</td>
<td>University of Louisville Research</td>
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<tr>
<td>Susan Coffin</td>
<td>Children's Hospital of Philadelphia</td>
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<td>Xiaoyan Song</td>
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APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

1. * TYPE OF SUBMISSION
   [X] Application  [ ] Changed/Corrected Application

2. DATE SUBMITTED
   02/19/2010  Applicant Identifier: 0006394

5. APPLICANT INFORMATION
   * Organizational DUNS: 001910777
   * Legal Name: Johns Hopkins University
   * Street1: 733 N. Broadway Street, Suite 117
   * Street2: Office of Research Administration
   * City: Baltimore  County / Parish:  
   * State: MD: Maryland  Province:  
   * Country: USA: UNITED STATES  * ZIP / Postal Code: 21205-1832

Person to be contacted on matters involving this application
Prefix:  * First Name: Marissa  Middle Name:  
* Last Name: Pio Roda  Suffix:  
* Phone Number: 4106140257  Fax Number: 4105027832
Email: mpioroda@johns Hopkins.edu

6. * EMPLOYER IDENTIFICATION (EIN) or (TIN):  

7. * TYPE OF APPLICANT:  
   [ ] Private Institution of Higher Education
   [ ] Other (Specify):  

Small Business Organization Type  [ ] Women Owned  [ ] Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
   [X] New  [ ] Resubmission
   [ ] Renewal  [ ] Continuation  [ ] Revision
   If Revision, mark appropriate box(es).
   [ ] Increase Award  [ ] Decrease Award  [ ] Increase Duration  [ ] Decrease Duration
   [ ] Other (specify):  

* Is this application being submitted to other agencies?  Yes  No  What other Agencies?  

9. * NAME OF FEDERAL AGENCY:
   [ ] NATL INST OF HEALTH
   [ ] 10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
   [ ] TITLE: NIH Small Research Grant Program (Parent RO3)

11. * DESCRIPTIVE TITLE OF APPLICANT’S PROJECT:
    Catheter Dwell Time and Risk of Bloodstream Infections in Hospitalized Neonates

12. PROPOSED PROJECT:
   * Start Date: 12/01/2010  * Ending Date: 11/30/2012  MD-007

13. CONGRESSIONAL DISTRICT OF APPLICANT

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION
   Prefix:  * First Name: Aaron  Middle Name:  
   * Last Name: Milstone  Suffix:  
   Position/Title: Assistant Professor
   * Organization Name: Johns Hopkins University
   * Street1: 200 N Wolfe St
   * Street2: Rubenstein 3141
   * City: Baltimore  County / Parish:  
   * State: MD: Maryland  Province:  
   * Country: USA: UNITED STATES  * ZIP / Postal Code: 21237
   * Phone Number: 4432878932  Fax Number:  
   * Email: amilstone@johns Hopkins.edu
### 15. Estimated Project Funding

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### 16. * Is Application Subject to Review by State Executive Order 12372 Process?

- **Yes**
  - **DATE:** [ ]
  - THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

- **No**
  - **PROGRAM IS NOT COVERED BY E.O. 12372; OR**
  - **PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW**

### 17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

- **I agree**
  - * The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

### 18. SFLII or other Explanatory Documentation

- [Add Attachment] [Delete Attachment] [View Attachment]

### 19. Authorized Representative

- **Prefix:** [ ]
- **First Name:** Amy
- **Middle Name:** Butler
- **Last Name:** Rost
- **Position/Title:** Grants Associate
- **Organization:** Johns Hopkins University
- **Department:** RESEARCH ADMINISTRATION
- **Street 1:** 133 N Broadway, Ste 117
- **City:** Baltimore
- **State:** MD: Maryland
- **Country:** USA: UNITED STATES
- **ZIP / Postal Code:** 21205
- **Phone Number:** 4105022150
- **Fax Number:** 4105027832
- **Email:** rrost1@jhu.edu

- **Signature of Authorized Representative:**
  - Rost, Amy B

- **Date Signed:** 02/19/2016

### 20. Pre-application

- [Add Attachment] [Delete Attachment] [View Attachment]
# 424 R&R and PHS-398 Specific Table Of Contents

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<td>Performance Sites</td>
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<td>Research &amp; Related Other Project Information</td>
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<td>Facilities &amp; Other Resources</td>
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**Project/Performance Site Location(s)**

**Project/Performance Site Primary Location**

☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

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<td>Street2:</td>
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RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved?  ☒ Yes  ☐ No

1.a. If YES to Human Subjects
   Is the Project Exempt from Federal regulations?  ☓ Yes  ☒ No
   If yes, check appropriate exemption number.  ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6
   If no, is the IRB review Pending?  ☒ Yes  ☐ No
   IRB Approval Date:
   Human Subject Assurance Number:

2. * Are Vertebrate Animals Used?  ☒ Yes  ☐ No

2.a. If YES to Vertebrate Animals
   Is the IACUC review Pending?  ☐ Yes  ☒ No
   IACUC Approval Date:
   Animal Welfare Assurance Number:

3. * Is proprietary/privileged information included in the application?  ☒ Yes  ☐ No

4.a. * Does this project have an actual or potential impact on the environment?  ☒ Yes  ☐ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?  ☒ Yes  ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place?  ☒ Yes  ☐ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators?  ☒ Yes  ☐ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract  M-5_Project_Summary.pdf  Add Attachment  Delete Attachment  View Attachment

8. * Project Narrative  M-1_Narrative.pdf  Add Attachment  Delete Attachment  View Attachment

9. Bibliography & References Cited  M-4_Bibliography_and_References_Cited.pdf  Add Attachment  Delete Attachment  View Attachment

10. Facilities & Other Resources  M-2_Facilities.pdf  Add Attachment  Delete Attachment  View Attachment

11. Equipment  M-3_Equipment.pdf  Add Attachment  Delete Attachment  View Attachment

12. Other Attachments  Add Attachments  Delete Attachments  View Attachments  ☐
Abstract

Intravenous (IV) access is essential to provide fluids, medications and nutrition to hospitalized neonates. Since the 1980s, peripherally inserted central venous catheters (PICC) have been increasingly used to provide IV access. PICCs can be placed at the bedside without general anesthesia and can remain in place for days or weeks with seemingly minimal mechanical complications. However, complications do occur, including central-line associated bloodstream infections (CLA-BSI), phlebitis, cellulitis, and thrombosis. CLA-BSIs have a significant attributable cost and an associated mortality of up to 20%. The long-term objective of this research is to further develop evidence-based strategies to prevent central-line associated bloodstream infections (CLA-BSI) among infants hospitalized in the neonatal intensive care unit. This proposal builds a multicenter pediatric collaborative to examine the association between catheter dwell time and CLA-BSI in this unique population.

Many studies have shown that the longer a catheter remains in the place, the greater the risk of complication. However, healthcare providers assume that the risk of a complication is constant from day to day. We hypothesize that 1) the daily risk of PICC-associated CLA-BSI in children hospitalized in the neonatal intensive care unit (NICU) is not constant, and 2) approximately one month after PICC insertion, a threshold exists beyond which time the daily risk of CLA-BSI significantly increases. This proposal will determine if the risk of PICC-associated CLA-BSI is constant over catheter dwell time, and identify whether a threshold exists beyond which the daily risk of CLA-BSI significantly increases. To complete this project we will perform a multicenter retrospective cohort study to collect and characterize data from seven tertiary care NICUs. We will evaluate risk factors for PICC-associated CLA-BSI, focusing on catheter dwell time as a non-linear independent predictor of CLA-BSI.

PICCs are essential to the care of hospitalized neonates, but CLA-BSI have significant mortality and associated financial costs. Neonates may face unnecessary risk from prolonged PICC duration if the risk of CLA-BSI over time is not constant. As PICCs continue to be used widely in other healthcare settings and populations, findings from this collaborative project should stimulate additional studies to improve quality of care and prevent healthcare-associated infections. Our long-term goal is to provide evidence-based justification for instituting preventive measures which could save lives and reduce healthcare costs.
Relevance
Bloodstream infections are a significant cause of morbidity and financial costs. This project will help to develop evidence-based strategies to prevent bloodstream infections among vulnerable infants hospitalized in the neonatal intensive care unit.
Facilities and Other Resources

Johns Hopkins Medical Institutions – Coordinating Center

The proposed research will take place at The Johns Hopkins Medical Institutions. Supporting Dr. Milstone’s will be the Division of Pediatric Infectious Diseases, the Department of Epidemiology and Infection Control, the Bloomberg School of Public Health, and collaborating sites.

The Division of Infectious Diseases, Department of Pediatrics
The Division of Infectious Diseases in the Department of Pediatrics has 6 full time faculty members all of whom are involved in intensive scientific investigation. The Division has a strong history of nurturing young investigators and providing them with the resources necessary to develop into independent investigators of international reputation. In the last 12 months the Division has generated over $8.8 million in direct cost and Division members have over 93 articles in peer-reviewed journals and book chapters on a variety of infectious diseases issues from both clinical and laboratory investigations.

The JHH Department of Epidemiology and Infection Control
The JHH Department of Hospital Epidemiology and Infection Control (HEIC) includes three physician epidemiologists who are also faculty in the School of Medicine, a senior nurse epidemiologist/manager, eight trained infection control nurses, and an information technology and data management specialist. Dr. Trish Perl is the director of HEIC, the Hospital Epidemiologist, and the former president of the Society for Healthcare Epidemiology of America. The trained infection control practitioners perform prospective surveillance for catheter-related bloodstream infections in the intensive care units. Their expertise in applying these definitions will be readily available to the investigators. HEIC uses standard CDC surveillance definitions. Annual rates of site-specific infections or for specific organisms are compared to the previous year’s rates and presented with 95% confidence intervals. Also, rates are compared to National Healthcare Surveillance Network (NHSN) when appropriate. HEIC works in parallel with the physician directed Antibiotic Management Program (AMP). AMP employs a pharmacist trained in infectious diseases who participates in the efforts to assure appropriate antimicrobial use within the institution. In addition, AMP reviews the trends in antimicrobial use over time to develop interventions. All of these programs utilize personal computers, network hard-drives, and institutional databases and information systems to maintain data and perform required functions. HEIC and AMP have sophisticated computer applications to obtain real-time access to microbiology and pharmacy data.

The HEIC research group is led by a master’s level research coordinator who oversees research assistants and fellows. The group has extensive experience with data management related to hospital epidemiology data. This group has participated in data sharing for many multicenter studies, including serving as the coordinating center for a large pediatric clinical trial. The institution’s information technology (IT) group supports and maintains networks, trouble-shoots application errors, performs daily back-ups, and conducts recoveries as needed.

The Bloomberg School of Public Health
The Bloomberg School of Public Health is the largest school of public health in the world, consisting of 530 full-time and 620 part-time faculty members. The School contains more than 50 centers and institutions including the Welch Center. The School is strongly dedicated both to public health research and to education of scientists and practitioners. Research within this entity spans to more than 90 countries and currently has 2,005 students from 83 nations. The Department of Biostatistics at the School of Public Health offers comprehensive consulting services for study design and analysis for the faculty, staff and trainees of the School of Medicine.

All co-investigators have extensive experience in clinical care as well as the epidemiology of healthcare-associated infections such as CLA-BSI (Drs. Coffin, Song, Smith, Saiman, Livingston, Huskins, and Bryant). These experts will oversee data collection at collaborating sites. These sites provide excellent support structure to facilitate data collection and management. Details of each site are listed below.
The Children's Hospital of Philadelphia (CHOP)

CHOP is a tertiary-care pediatric institution affiliated with The University of Pennsylvania and is located in Philadelphia, PA where it serves as a community hospital for the children of West Philadelphia as well as an international referral hospital. CHOP is a free-standing, 430 bed hospital that includes a 75 bed neonatal intensive care unit (NICU), 45 bed pediatric intensive care unit (PICU), a 26 bed cardiac intensive care unit (CICU), and approximately 280 medical/surgical beds. Some of the specialties offered at CHOP include Fetal Diagnosis and Treatment, Cardiac Care, Oncology, Transplant and Neonatology. All of CHOP's ICUs have the capability to provide extra corporeal membrane oxygenation (ECMO).

Founded in 1855, The CHOP is the nation’s oldest hospital dedicated solely to the care of children. The hospital's overall mission is the advancement of health care for children through excellent patient care, innovative research and education. In June 2008, for the sixth consecutive year, CHOP was ranked as the number one hospital for children in the nation by U.S. News and World Report. In addition, CHOP ranked number one in Cancer, Neonatal Care, and Respiratory Disorders, second in Heart and Heart Surgery, and Digestive Disorders, and ranked third in Neurology and Neurosurgery. CHOP has also been ranked as the number one pediatric hospital by Child Magazine every year from 2001 through 2007.

CHOP provides accessible, comprehensive, innovative and high quality medical and surgical care to children in Pennsylvania, New Jersey, Delaware and other states and countries. It is the community hospital and primary care center for children of West and South Philadelphia, and is a major tertiary referral center for the greater Delaware Valley, which has an estimated population of 10 million. The heart of CHOP’s network is its main campus complex in University City, consisting of the 430-bed main hospital devoted primarily to inpatient care; the Leonard and Madlyn Abramson Pediatric Research Center, home to the Joseph Stokes, Jr. Research Institute; the Richard D. Wood Pediatric Ambulatory Care Center; the Children's Seashore House, a medical care and rehabilitation facility for children with chronic illnesses and severe disabilities; and the General Pediatric Faculty Practice where hospital faculty and staff provide primary care to children from the Philadelphia area. In FY 2006, CHOP had 24,048 inpatient admissions accounting for 118,614 patient days.

Infection Prevention & Control

CHOP's Department of Infection Prevention & Control is committed to preventing adverse outcomes such as health care associated infections and related events. They strive to improve patient care by supporting the staff in all areas of the facility when appropriate, to minimize occupational hazards associated with the delivery of health care, and to foster scientific-based decision-making. The infection control practitioners have many years of experience in monitoring catheter-associated blood steam infections (CA-BSI) in all areas of the hospital, including the NICU, and submitting data to the National Healthcare Surveillance Network (NHSN) and other reporting systems.

Patient Information/Information Technology Systems

CHOP has an electronic medical record that will provide the demographic and clinical data needed for this project (Chartmaxx). All microbiological data will be obtained using laboratory-specific software (Meditech). Master lists and databases will be maintained using Microsoft Office 2007 software.

Children's National Medical Center

For more than 130 years, Children's National Medical Center (CNMC) has provided primary care as well as cutting-edge clinical services to multiple generations of the nation's children. CNMC comprises of 6 entities including: 1) Children's Hospital featuring 283 beds, 4 intensive care units for neonates, pediatric, cardiac surgery, and neurological services; and one Emergency Department with a Level I pediatric trauma center; 2) six Regional Outpatient Centers; 3) A primary care program that includes health centers within the District of Columbia and privately owned practices throughout the metropolitan area; 4) Children's National Health Network with 400 affiliated pediatricians; 5) Children's Research Institute which is a leader in basic
and clinical research programs; and 6) Other subsidiaries that focus on school health services, mobile health services, community partnerships, and safety campaigns. The comprehensive infrastructure of CNMC enables its clinicians, educators, and staff to reach underserved children living in the neighborhood with limited or no health insurances, and reflects its vision of providing continuity of care for the most vulnerable among us: our children.

The Office of Infection Control program at CNMC has 3 full-time certified Infection Control Practitioners. CNMC has been a member of National Healthcare Safety Network (NHSN, formerly National Nosocomial Infection Surveillance study - NNIS) for over a decade. At CNMC, surveillance for central-line associated bloodstream infections has been conducted using the NHSN definition. In May 2008, a computerized provider order entry system (PowerChart, Cerner©) was implemented in inpatient units. Care providers document information related to a central line use such as type of central line, date of insertion and discontinuation, and insertion site. The information is viewable for data extraction or can be downloaded electronically.

Duke University Medical Center (DUMC)

The proposed research will take place at Duke University Medical Center (DUMC), a large tertiary-care university-affiliated hospital located in Durham, North Carolina. The DUMC neonatal intensive care unit (NICU) is a 54 bed level III NICU. Our institution has sophisticated computer programs and support to obtain the needed microbiology and patient level data for this project. Data is available through electronic medical records as well as Duke Enterprise Data Unified Content Explorer (DEDUCE) – an on-line research tool providing Duke investigators with access to clinical information collected as a by-product of patient care. The DEDUCE project is funded by the NIH sponsored Duke Translational Medical Institute (DTMI), and is intended to facilitate exploration of aggregate clinical data in support of operations, quality and research. DEDUCE compiles its data from multiple source systems, and allows the researcher to filter through millions of rows of data to define a clinical cohort and streamline electronic chart review. Current data sources include lab data, demographics, ICD-9 diagnoses, procedures, inpatient medications, microbiology results, and physician orders. The DEDUCE system has limited access and significant security. A separate electronic system is available for insertion and removal data for all PICC lines placed at DUMC. We have trained infection control practitioners perform prospective surveillance for catheter-related bloodstream infections in the NICU.

Mayo Eugenio Litta Children’s Hospital

The proposed study will take place at the Mayo Eugenio Litta Children’s Hospital in Rochester, Minnesota. The hospital is a 92 bed hospital, including a 30 bed neonatal intensive care unit and a 20 bed pediatric intensive care and transplant unit.

Dr. Huskins supervises all activities related to the surveillance of healthcare-associated infections. Infection control professionals perform case finding by laboratory-based surveillance, including review of all positive blood cultures. Dr. Huskins reviews each case to determine that it satisfies the definitions used by the National Healthcare Surveillance Network (NHSN). Cases are recorded in an electronic database that can be queried to identify all potential research subjects for this study. Mayo Clinic has a complete electronic medical record that can be used to collect the demographic and microbiological data needed for this project.

Kosair Children’s Hospital

The proposed study will take place at Kosair Children’s Hospital (KCH) a tertiary-care university-affiliated hospital located in Louisville, KY. KCH is a 257 bed hospital that includes a 97-bed neonatal intensive care
unit and 26 bed pediatric intensive care. Both units have the capacity to provide extra corporeal membrane oxygenation (ECMO).

We have 4 infection preventionists, one of whom is assigned solely to NICU infection prevention and surveillance. A clinical nurse specialist assists with infection prevention efforts in the NICU. Patients with central lines, including percutaneously inserted central catheters, are identified prospectively and duration of catheterization is captured in a designated database. Catheter-associated blood stream infections (CA-BSI) are reported to National Healthcare Surveillance Network (NHSN). Other sources of demographic and microbiologic data for this study include the institution’s electronic medical record as well as a web-based surveillance tool (Quality Compass®).

Children’s Mercy Hospital

The proposed study will take place at the Children’s Mercy Hospital (CMH) & Clinics, a tertiary-care university-affiliated hospital located in Kansas City, Missouri and a lower acuity hospital located in Overland Park, Kansas. CMH is a 317 bed hospital that includes a 64 bed neonatal intensive care unit, 27 bed pediatric intensive care unit, and 226 medical/surgical beds. Programs include solid organ and bone marrow transplant with specialized clinics caring for patients with human immunodeficiency virus, cystic fibrosis, and end stage renal disease. CMH has an in-house pediatric dialysis unit and the capability to provide extra corporeal membrane oxygenation (ECMO) in both of our intensive care units.

Our infection control practitioners have many years of experience in monitoring catheter-associated blood steam infections (CA-BSI) in all areas of the hospital including home care and submitting data to the National Healthcare Surveillance Network (NHSN). Our institution has an electronic medical record that will provide the demographic and microbiological data needed for this project as well as a database containing all potential research subjects for this study.

Morgan Stanley Children’s Hospital of NewYork-Presbyterian at Columbia University Medical Center

The proposed research will take place at the Morgan Stanley Children’s Hospital of NewYork-Presbyterian at Columbia University Medical Center located in New York City. The Morgan Stanley Children’s Hospital of NewYork-Presbyterian, was founded in 1867 and was the first hospital established for infants and children in the United States. It is internationally recognized for its research and clinical resources and was cited in an NIH-sponsored study published in the journal Pediatrics as a center for excellence both in research and in patient care. Our NICU ranks among the top 10 NICUs in the US and is a center of excellence for neonatology and maternal/fetal care. The NICU has 62 beds and there are approximately 1100 annual admissions including both preterm infants and full term infants with complex congenital anomalies requiring surgical interventions. Our institution has an electronic medical record system, Eclypsis, which captures patient level demographic, clinical, laboratory, and treatment data.

Our Department of Infection Prevention and Control has extensive information technology resources. Most notably, our department and Columbia University’s Department of Biomedical Informatics developed an automated surveillance system, EpiPortal, which integrates information from disparate systems (e.g., laboratory, pharmacy, and electronic medical records) within a single access, web-based screen. EpiPortal allows analytical queries of population- and temporally-based data which are used to support infection control initiatives and research studies. Our department is responsible for fulfilling New York State mandatory healthcare-acquired infections surveillance reporting that, since January 2008, includes central line-associated bloodstream infections (CLABSIs) in intensive care units (adult, pediatric and neonatal intensive care units) and umbilical catheter-associated infections in neonates. NYS uses the National Healthcare Safety Network and case definitions for reporting CLABSIs.
Equipment

N/A
### RESEARCH & RELATED Senior/Key Person Profile (Expanded)

**PROFILE - Project Director/Principal Investigator**

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**RESEARCH & RELATED Senior/Key Person Profile (Expanded)**

### PROFILE - Senior/Key Person 2

- **Prefix:**
- **First Name:** Susan
- **Middle Name:**
- **Last Name:** Coffin
- **Position/Title:** Associate Professor
- **Department:**
- **Organization Name:** Children's Hospital of Philadelphia
- **Division:** SCHOOL OF MEDICINE
- **Street:** 3615 Civic Center Boulevard
- **City:** Philadelphia
- **State:** PA: Pennsylvania
- **Country:** USA: UNITED STATES
- **Phone Number:** 215-590-4492
- **E-Mail:** coffin@email.chop.edu
- **Credential:**
- **Project Role:** Other (Specify)
- **Other Project Role Category:** Co-investigator
- **Degree Type:**
- **Degree Year:**

### PROFILE - Senior/Key Person 3

- **Prefix:**
- **First Name:** N.
- **Middle Name:** Charles
- **Last Name:** Huskins
- **Position/Title:** Assistant Professor
- **Department:**
- **Organization Name:** Mayo Clinic
- **Division:** SCHOOL OF MEDICINE
- **Street:** 200 First Street SW
- **City:** Rochester, Minnesota
- **State:** MN: Minnesota
- **Country:** USA: UNITED STATES
- **Phone Number:** 507-284-2511
- **E-Mail:** huskins.charles@mayo.edu
- **Credential:**
- **Project Role:** Other (Specify)
- **Other Project Role Category:** Co-investigator
- **Degree Type:** N.D.
- **Degree Year:** 1986

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**Key Personnel**

Page 14
**RESEARCH & RELATED Senior/Key Person Profile (Expanded)**

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| Degree Type: | M.D. |
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**Key Personnel**

Page 15
RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 6
Prefix: 
* First Name: P. Brian 
Middle Name: 
* Last Name: Smith 
* Suffix: 
Position/Title: Assistant Professor 
Department: 
Organization Name: Duke University 
Division: SCHOOL OF MEDICINE 
* Street1: PO Box 17969 
Street2: 
* City: Durham 
County/Parish: 
* State: NY: New York 
Province: 
* Country: USA: UNITED STATES 
* Zip/Postal Code: 27715 
* Phone Number: (919) 685-8951 
Fax Number: 
* E-Mail: brian.smith@duke.edu 
Credential, e.g., agency login: [GSA Commons User Name] 
* Project Role: Other (Specify) 
Other Project Role Category: Co-Investigator 
Degree Type: M.D. 
Degree Year: 2001 
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PROFILE - Senior/Key Person 7
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* First Name: Xiaoyan 
Middle Name: 
* Last Name: Song 
* Suffix: 
Position/Title: Assistant Professor 
Department: 
Organization Name: George Washington University 
Division: SCHOOL OF MEDICINE 
* Street1: 111 Michigan Ave, NW 
Street2: 
* City: Washington 
County/Parish: 
* State: DC: District of Columbia 
Province: 
* Country: USA: UNITED STATES 
* Zip/Postal Code: 20010 
* Phone Number: 202-476-5000 
Fax Number: 
* E-Mail: ksong@cmc.org 
Credential, e.g., agency login: [GSA Commons User Name] 
* Project Role: Other (Specify) 
Other Project Role Category: Co-Investigator 
Degree Type: MBBS 
Degree Year: 1992 
*Attach Biographical Sketch: ID-2059_EN-1_BIOSKETCH.pdf 
Attach Current & Pending Support: 

Key Personnel
Page 16
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
Milstone, Aaron Michael

POSITION TITLE
Assistant Professor of Pediatrics

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

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(S)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington University, St. Louis, MO</td>
<td>B.A.</td>
<td>1991-1995</td>
<td>Political Science</td>
</tr>
<tr>
<td>Yale School of Medicine, New Haven, CT</td>
<td>M.D.</td>
<td>1995-2000</td>
<td>Medicine</td>
</tr>
<tr>
<td>Children’s Hospital of Philadelphia, PA</td>
<td>Intern/Resident</td>
<td>2000-2003</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Children’s Hospital of Philadelphia, PA</td>
<td>Postdoc</td>
<td>2003-2004</td>
<td>Ped. Infectious Diseases</td>
</tr>
<tr>
<td>Johns Hopkins University School of Medicine, MD</td>
<td>Fellow</td>
<td>2004-2007</td>
<td>Ped. Infectious Diseases</td>
</tr>
<tr>
<td>Johns Hopkins University School of Public Health, MD</td>
<td>MHS</td>
<td>2007-2009</td>
<td>Clinical Investigation</td>
</tr>
</tbody>
</table>

A. Personal Statement

The goal of the proposed research is to develop evidence-based strategies to prevent central-line associated bloodstream infections (CLA-BSI) in hospitalized children. Specifically, this proposal builds a multicenter pediatric collaborative to focus on the association between catheter duration and CLA-BSI. I have the leadership, experience, and determination to complete this project. With my mentor Dr. Trish Perl, I am leading a multicenter randomized controlled clinical trial in the pediatric intensive care unit testing a novel strategy to reduce CLA-BSI. Though this study, we have experience with submitting protocols to multiple IRBs, communicating through weekly conference calls, and collecting and merging data from multiple hospitals. I was the PI of a study recently completed at our institution that evaluated the association between catheter duration and CLA-BSI in the neonatal intensive care unit. During that study, we developed a data management infrastructure and a solid biostatistical model to approach the proposed research question. We have selected collaborators with easily accessible data, and we have experience collaborating with most of them. This proposal is the appropriate next step to obtain confirmatory evidence and lay the scientific and collaborative foundation for a definitive prospective study. I have a record of successful and productive research endeavors, this research topic is timely and of great public health interest.

B. Positions and Honors

Positions and Employment

2001-2003 Instructor, Department of Pediatrics, University of Pennsylvania School of Medicine
Philadelphia, PA

2003-2004 Attending Physician, Division of Emergency Medicine, Sections of Urgent Care and Emergency Transport, Children’s Hospital of Philadelphia, Philadelphia, PA

2007-present Assistant Professor, Department of Pediatrics, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD

2008-present Infection Control Officer, Co-Chairperson of the Kennedy Krieger Medical Staff Infection Control Committee, Kennedy Krieger Hospital, Baltimore, Maryland

Other Experience and Professional Memberships

2000-present Member, American Academy of Pediatrics

2004-present Member, Pediatric Infectious Disease Society

2004-present Member, Infectious Disease Society of America

2005 Ad Hoc reviewer Medicine

2007 Ad Hoc reviewer Journal of Urology

2007 Ad Hoc reviewer Journal of Clinical Pediatrics
2007-present  Member, Society of Healthcare Epidemiology of America  
2009  Ad Hoc reviewer Journal of Pediatric Dermatology  
2009-present  Ad Hoc reviewer Pediatric Infectious Disease Journal  
2010-present  Member, Society of Healthcare Epidemiology of America Research Committee  
2010  Ad Hoc reviewer Clinical Infectious Diseases  

**Honors and Awards**  
1998  Wilbur C. Downs International Travel Research Fellowship  
1999  Medical Student Research Training Fellowship  
2000  Election to Alpha Omega Alpha  
2000  Society for Pediatric Research Medical Student Research Award  
2005-2007  Pediatric Infectious Disease Society Fellowship Award  
2005  Infectious Disease Society of America Travel Award  
2007  Infectious Disease Society of America Travel Award  
2007-2009  Johns Hopkins Clinical Research Scholars K12 Award  
2010  Society for Healthcare Epidemiology of America Pediatric Investigator Award  

**C. Selected peer-reviewed publications (selected from 27 peer-reviewed publications)**  

**Most relevant to the current applicant**  
1.  

**Additional recent publications of importance to the field**  


D. Research Support

**Ongoing Research Support**

1 K23 AI081752-01 (Milstone, Aaron M.) 07/01/2009-06/30/2013

NIH/NIAID
MRSA in Children: Epidemiology, Pathogenesis, and Prevention
The goal of this grant is to define the epidemiology of MRSA in hospitalized children, to assess the impact of virulent MRSA strains of community-origin, and to test a novel method for MRSA control.
Role: PI

No assigned number (Milstone, Aaron M.) 10/01/2008-09/31/2010

*Early Identification of Respiratory Viruses in Hospitalized Neonates and Infants without Common Symptoms of Viral Illness*
The major goal of this project is measure the burden of respiratory viruses in hospitalized neonates with and without common symptoms of influenza-like illnesses.
Role: PI

No assigned number (Milstone, Aaron M.) 7/01/2008-06/30/2010

*Protecting children from the 'Superbug': A novel approach to preventing the spread of methicillin-resistant *Staphylococcus aureus* (MRSA)*
The major goal of this project is to assess a novel strategy to prevent MRSA transmission in the pediatric intensive care unit.
Role: PI

No assigned number (Perl, Trish M) 7/01/2007-09/30/2011
"Impact of Daily Bathing with Chlorhexidine Impregnated Cloths on Nosocomial Infections in the Pediatric Intensive Care Unit"
The major goal of this project is to assess a novel strategy to prevent MRSA transmission in the pediatric intensive care unit.
Role: Co-Investigator

Completed Research Support
1KL2RR025006-01 (Ford, Daniel)  10/01/2007-06/30/2009
NIH/NCRR
Clinical and Translation Science Award
One of this grant’s goals is to improve the training and career development of clinical/translational scientists.
Role: Scholar

K12RR023266  7/01/2007-9/30/2007
NIH/NCRR
Multidisciplinary Clinical Research Career Development Program
One of this grant’s goals is to improve the training and career development of clinical/translational scientists.
Role: Scholar

No assigned number (Milstone, Aaron M.)  7/01/2005-06/30/2007
Private Source
“Role of secreted protease inhibitors in Toxoplasma gondii infection.”
The goal of this grant was to identify novel virulence factors in T. gondii pathogenesis.
Role: PI
BIOGRAPHICAL SKETCH
Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow the sample format for each person. DO NOT EXCEED FOUR PAGES.

NAME
Kristina A. Bryant, M.D.

POSITION TITLE
Associate Professor

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

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(S)</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Louisville</td>
<td>B.A.</td>
<td>1987</td>
<td>French, Political Science</td>
</tr>
<tr>
<td>University of Louisville School of Medicine</td>
<td>M.D.</td>
<td>1994</td>
<td></td>
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</table>

A. Personal Statement:
I am the hospital epidemiologist and Infection Control Committee chairperson at Kosair Children’s Hospital in Louisville, KY. Our hospital conducts unit-specific surveillance for catheter infections, including in our 97 bed neonatal intensive care unit. Much of the data required for the proposed project is collected prospectively by a designated NICU infection preventionist. Reduction of catheter-associated infections in NICU patients is a key measure in our hospital’s annual quality improvement plan. I have experience working in multicenter collaboratives, and have collaborated with several of the co-investigators as part of the NACHRI Pediatric Intensive Care Unit Bloodstream Infection Prevention Collaborative.

B. Positions and Honors
1994
Alpha Omega Alpha

1994-1997
Resident in Pediatrics, University of Louisville, Louisville, KY

1997-2000
Kosair Charities Fellow, Pediatric Infectious Diseases, University of Louisville

2000-2008
Assistant Professor of Pediatrics, University of Louisville School of Medicine

2000-present
Hospital Epidemiologist, Kosair Children’s Hospital

2000-present
Pediatric Infectious Diseases Society
Member, Training Programs Committee, 2004-present
Chair, Training Programs Committee, 2008-present

2002-2002
Associate Medical Director, Just for Kids Hospitalist Program, Kosair Children’s Hospital

2002-2003
Medical Director, Just for Kids Hospitalist Program, Kosair Children’s Hospital

2004-present
Society for Healthcare Epidemiology of America
Member, Guidelines Committee, (2008-present)
Member, Public Policy and Governmental Affairs Committee (2009-present)

2004-present
Infection Control Physician Liaison, University of Louisville Hospital

2008-present
Infection Control Consultant, Home of the Innocents, Louisville, KY

2005-present
Adjunct Clinical Professor, Pikeville School of Osteopathic Medicine

2008-present
Pediatric Infectious Diseases Fellowship Director, University of Louisville

2008-present
Associate Professor of Pediatrics, University of Louisville

2009
Centers for Disease Control and Prevention Special Emphasis Panel

C. Selected peer-reviewed publications (in chronological order).


16. In Press

D. Research Support

Ongoing Research Support

Avian influenza pandemic preparedness: Observational study to evaluate the incidence of intensive care unit admission in patients hospitalized with community-acquired pneumonia in Kentucky.
The goal of this project is to develop and implement a comprehensive surveillance system in the Commonwealth of Kentucky for patients hospitalized in intensive care units with community-acquired pneumonia.
Role: Co-Investigator
2007-present
A phase 3, randomized, active-controlled, modified double-blind trial evaluating the safety, tolerability, and immunogenicity of a 13-Valent Pneumococcal conjugate vaccine (13vPnC) compared to a 23-valent pneumococcal polysaccharide vaccine (23vPS) in adults 60 to 64 Years old who are naive to 23vPS and the safety, tolerability, and immunogenicity of 13vPnC in Adults 50-59 Years Old who are Naive to 23vPS. Role: Principal Investigator

2007-present
A phase 3, randomized, active-Controlled, double-blind trial evaluating the safety, tolerability, and immunogenicity of 3 lots of 13-Valent pneumococcal conjugate vaccine in healthy infants given with routine pediatric vaccinations in the United States. Role: Principal Investigator

2008-present
Bryant K. A Phase 3, open-label, randomized, multi-center study to evaluate the safety and immunogenicity of ProQuad™ vaccine when administered concomitantly with Novartis Meningococcal ACWY conjugate vaccine to healthy toddlers. Role: Principal Investigator

2009-present
Bryant K. A phase 3 open-label trial evaluating the safety, tolerability and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy children aged 15 months to 17 yrs in the U.S. Role: Principal Investigator

2009-present
A phase 3, open-label, single-arm trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in children with sickle cell disease previously immunized with 23-valent pneumococcal polysaccharide vaccine. Role: Principal Investigator
BIOGRAPHICAL SKETCH

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

NAME
Susan E. Coffin, MD, MPH

POSITION TITLE
Associate Professor C-E

eRA COMMONS USER NAME

POSITION TITLE
Associate Professor C-E

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

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>YEAR(S)</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Williams College</td>
<td>B.A.</td>
<td>1983</td>
<td>History</td>
</tr>
<tr>
<td>University of Vermont College of Medicine</td>
<td>M.D.</td>
<td>1987</td>
<td></td>
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<tr>
<td>Johns Hopkins School of Hygiene and Public Health</td>
<td>M.P.H.</td>
<td>1991</td>
<td>Epidemiology</td>
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</table>

A. Personal Statement:
I am the hospital epidemiologist and medical director of the Infection Prevention and Control program at the Children's Hospital of Philadelphia. Our program conducts hospital-wide surveillance for catheter infections, including in our 75-bed neonatal intensive care unit. Our program also provides data to support our hospital-wide vascular access database that will be used as the source of data from our institution for the proposed project. I have previously worked with Dr. Milstone on other multi-center infection control research projects.

B. Positions and Honors
1987 Alpha Omega Alpha
1987-1992 Intern, Resident, Chief Resident in Pediatrics, Johns Hopkins Hospital, Baltimore, MD
1991 Delta Omega Alpha
1992-1997 Fellowship, Infectious Diseases, The Children's Hospital of Philadelphia (CHOP)
1995-present Member, The Joseph Stokes Research Institute, CHOP
1998-2007 Assistant Professor of Pediatrics, UPenn School of Medicine
2000-present Society for Healthcare Epidemiology of America, Member, Public Policy and Governmental Affairs Committee (2007-present)
2002-present Associate Scholar, Center for Clinical Epidemiology & Biostatistics, UPenn Sch. of Medicine
2003-present Hospital Epidemiologist; Medical Director, Infection Prevention and Control, CHOP
2004-present Faculty Member, Graduate Program in Public Health Studies, UPenn School of Medicine
2006-present Member, Center for Education and Research on Therapeutics, UPenn School of Medicine
2007-present Associate Professor of Pediatrics, UPenn School of Medicine
2007-present Associate Director, Center for Pediatric Clinical Effectiveness, CHOP

C. Selected peer-reviewed publications (in chronological order).
(15 publications selected from 60 peer-reviewed publications)


**D. Research Support**

**Ongoing Research Support**

RFP 05-07-11 Hildegard Ertl
State of Pennsylvania
Development of Universal Influenza A Virus Vaccine
Role: Site PI
R03 HD055966 Susan Coffin 09/01/07-08/31/10
NIH/NICHD
Impact of Oseltamivir on Outcomes and Costs of Pediatric Influenza
Role: PI

N01-AI-50024 Kathleen Sullivan 07/01/05-06/30/10
NIH/NIAID
Kinetic analysis of immunologic repletion and influenza vaccine responsiveness
Role: Project PI
BIOGRAPHICAL SKETCH
Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FOUR PAGES.

NAME
W. Charles Huskins

POSITION TITLE
Assistant Professor of Pediatrics, Mayo Medical School Consultant, Pediatric Infectious Diseases, Mayo Clinic

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

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford University, Stanford, CA</td>
<td>B.S.</td>
<td>1980</td>
<td>Biology</td>
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<tr>
<td>University of Minnesota Medical School, Minneapolis, MN</td>
<td>M.D.</td>
<td>1986</td>
<td>Medicine</td>
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<tr>
<td>Children's Hospital, Boston, MA</td>
<td></td>
<td>1986-89</td>
<td>Residency in Pediatrics</td>
</tr>
<tr>
<td>Children's Hospital, Boston, MA</td>
<td></td>
<td>1989-92</td>
<td>Fellowship in Pediatric Infectious Diseases</td>
</tr>
<tr>
<td>Harvard School of Public Health, Boston, MA</td>
<td>M.Sc.</td>
<td>1998</td>
<td>Epidemiology</td>
</tr>
</tbody>
</table>

A. Personal Statement
I have more than 15 years experience in pediatric infectious diseases and healthcare epidemiology. For the past 10 years I have overseen all activities related to surveillance of healthcare associated infections in children hospitalized in the Mayo Eugenio Litta Children's Hospital and personally review each case of catheter-associated bloodstream infection. I have extensive experience in healthcare epidemiology and prevention research, including serving as the infectious diseases expert on the faculty of the National Association of Children’s Hospitals and Related Institution’s Pediatric Critical Care Medicine Eradicating Catheter-Associated Bloodstream Infection project—a multicenter improvement collaborative now involving more than 60 pediatric intensive care units nationwide. In February 2010, the initial results of the project demonstrating a 43% reduction in bloodstream infection rates were published. Although significant progress has been made in reducing catheter-associated bloodstream infections in pediatric patients, host and care-related factors make critically ill neonates in neonatal intensive care units especially vulnerable to these infections. The information related to the risk of infection associated with dwell time of intravascular catheters in this population generated during the course of this study will be critical in moving prevention efforts forward. Dr. Milstone and I are currently collaborating on a variety of projects.

B. Positions and Honors
1992 – 00  Instructor of Pediatrics, Harvard Medical School, Boston, MA
1992 – 00  Assistant in Medicine (Infectious Diseases), Children's Hospital, Boston, MA
2000  Assistant Professor of Pediatrics, Harvard Medical School, Boston, MA
2000 – 03  Senior Associate Consultant, Department of Pediatric and Adolescent Medicine, Division of Pediatric Infectious Diseases and Department of Internal Medicine, Division of Infectious Diseases, Mayo Clinic, Rochester, MN
2001 – 04  Assistant Director for Research Education and Training, Mayo General Clinical Research Center, Rochester, MN
2000  –  Assistant Professor of Pediatrics, Mayo Clinic College of Medicine, Rochester, MN
2000 –  Hospital Epidemiologist, Mayo Eugenio Litta Children's Hospital, Rochester, MN
2003 –  Consultant, Department of Pediatric and Adolescent Medicine, Division of Pediatric Infectious Diseases and Department of Internal Medicine, Division of Infectious Diseases, Mayo Clinic, Rochester, MN
2004 – 2006  Associate Director for Research Education and Training, Mayo General Clinical Research Center, Rochester, MN
2007 –  Associate Director for Education Resources, Mayo Clinic Center for Translational Science Activities, Rochester, MN
Other Experience and Professional Memberships

2001 – 2007 **Member**, Research Committee, Host Risk Group 4; Intensive Care Unit Patients at Risk for Serious Health-Care Associated Antimicrobial Resistant Bacterial Infections; Bacteriology and Mycology Study Group; National Institute of Allergy and Infectious Diseases

2001 – 2009 **Liaison**, Pediatric Infectious Diseases Society to the Infectious Diseases Society of America Practice Guideline Committee


2002 **Member**, National Institutes of Health National Center for Research Resources, Special Emphasis Panel 2002/10 Council ZRR1 CR-7 (01), June 4-5, 2002

2002 **Member**, Centers for Disease Control and Prevention, National Center for Infectious Disease, Special Emphasis Panel on Antimicrobial Resistance, Applied Research on Antimicrobial Resistance (Announcement Number 02175), August 22, 2002

2004 **Fellow**, Society for Healthcare Epidemiology of America

2005 **Member**, Centers for Disease Control and Prevention, National Center for Infectious Disease/Office of the Director, Special Emphasis Panel/Initial Review Group, Epi-Centers for Prevention of Healthcare-Associated Infections, 2006/08 ZCI1 TYM (10), December 9, 2005

2006 **Member**, Society for Pediatric Research

2007 **Consultant**, Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health, A Public Health Action Plan to Combat Antimicrobial Resistance, December 12-13, 2007


Honors

1980 Phi Beta Kappa
1984 Alpha Omega Alpha
1984 – 85 American Heart Association Medical Student Research Fellowship
1990 Massachusetts Society of Infectious Diseases, Edward H. Kass Award for Clinical Excellence
2004 – 05 Outstanding Educator, Mayo Clinic

C. Selected peer-reviewed publications (in chronological order).

Most relevant to the current application


Additional recent publications of importance to the field (in chronological order)


D. Research Support.

Ongoing Research Support
UL1 RR-24150 (Rizza, PI) 09/30/2006-06/30/2011
NIH/NCRR

The Mayo Clinic Center for Clinical and Translational Science Activities (CTSA)
The goal of this application is to integration and expand our innovative clinical and translational research activities, so that a highly functional academic home for clinical and translational research is developed at the Mayo Clinic. This new Mayo Clinic Center for Clinical and Translational Science Activities (CTSA) will include: 1) Clinical Research Core Resources that provide innovative tools to investigator; 2) Career Development and Education Programs that prepare the next generation of investigators; 3) Compliance and Regulatory Affairs Support that ensures patient safety and privacy, and enhance participation, diversity and community support for clinical and translational research, and 4) Continued and expanded institutional support that includes an "academic home" for clinical and translational research.
Role: Associate Director, Career Development and Education Programs

Completed Research Support
N01 AI-15440 (Dismukes) 04/8/2001-04/07/2007
NIH/NIAID

Bacteriology and Mycology Study Group (BAMSG)
Division of Microbiology and Infectious Diseases (DMID) Protocol Number 02-081, Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Adult Intensive Care Units
The major goal of the BAMSG is to coordinate a multi-center collaborative clinical trials network for evaluating interventions for serious fungal and health-care associated antimicrobial resistant bacterial infections and to develop a research agenda along current public health initiatives.
Role: Protocol Chair, for the Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Adult Intensive Care Units (STAR*ICU) trial
The STAR*ICU trial is a multi-center cluster-randomized clinical trial conducted through the BAMSG and is designed to evaluate the efficacy of two infection control strategies in reducing colonization and infection with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* in adult ICUs.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/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
Livingston, Robyn Ann

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable."

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Memphis, Memphis, TN</td>
<td>BS</td>
<td>1990-1994</td>
<td>Biology</td>
</tr>
<tr>
<td>University of Tennessee, Memphis, TN</td>
<td>MD</td>
<td>1995-2001</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of Louisville &amp; Kosair Children's Hospital, Louisville, KY</td>
<td></td>
<td>2001-2004</td>
<td>Residency in Pediatrics</td>
</tr>
<tr>
<td>University of Louisville, Division of Pediatric Infectious Diseases &amp; Kosair Children's Hospital</td>
<td></td>
<td>2004-2007</td>
<td>Pediatric Infectious Diseases Fellowship</td>
</tr>
</tbody>
</table>

A. Personal Statement

The goal of this study is to determine the association between central line duration and the risk of central-line-associated blood stream infections (CLA-BSI) in the neonatal intensive care unit (NICU). I am well suited for this project as I have three years of experience in Hospital Epidemiology and Infection Control and function as the Director of Infection Control & Prevention at Children’s Mercy Hospital & Clinics. In my current role, I work closely with our Infection Control Team, Vascular Access, and our intensive care units to help determine preventive strategies for decreasing CLA-BSI’s in our institution. I am the site principal investigator for the National Children’s Hospital and Related Institutions (NACHRI) Blood Stream Infection (BSI) Collaborative, a national study to determine best practices for decreasing CLA-BSI’s in the pediatric intensive care unit (PICU). I look forward to participating in this collaborative in an endeavor to determine further strategies to decrease CLA-BSI’s in the NICU population.

B. Positions and Honors

HOSPITAL APPOINTMENT
2007-present Children’s Mercy Hospital & Clinics, Kansas City, Missouri & Overland Park, Kansas
Director, Infection Control & Prevention

ACADEMIC APPOINTMENT
2007-present Assistant Professor of Pediatrics
University of Missouri at Kansas City, School of Medicine

AWARDS

C. Selected Peer-reviewed Publications

D. Research Support

**Ongoing Research Support**

1. **Private Source**
   Harrison (PI) 03/2007-open
   A Phase 1, Open-Label Study of the Safety of Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Children (2-5 Years and 6-11 Years) and Adolescents (12-16 Years) with Esophageal Candidiasis or Other Invasive Infections.
   Role: Co-Investigator

2. **Private Source**
   Harrison (PI) 05/2008-open
   A phase II randomized, observer blind, multicenter study of GlaxoSmithKline Biologicals' combined measles-mumps-rubella-varicella vaccine (MMRV) versus ProQuad®, according to a one-dose schedule. Both administered subcutaneously at 12-14 months of age, concomitantly with hepatitis A vaccine (HAV) and pneumococcal conjugate vaccine (PCV) but at separate sites.
   Role: Co-Investigator

4. University of Alabama at Birmingham Harrison (PI) 01/2010-open
   A Phase III Randomized, Placebo-Controlled Blindened Investigation of Six Weeks Vs. Six Months of Oral Valganciclovir Therapy in Infants with Symptomatic Congenital Cytomegalovirus Infection. Collaborative Antiviral Study Group (CASG) Central Unit
   Role: Co-Investigator

5. **Private Source**
   Harrison (PI) 08/2009-open
   A Phase II Study in Infants (≥6- <36 months), Children (≥36 months – 9 years), and Adolescents (10 – 17 years) to Assess the Safety and Immunogenicity of an Unadjuvanted Sanofi Pasteur H1N1 Influenza Vaccine Administered at Two Dose Levels.
   Role: Co-Investigator

**Completed Research Support**

1. **Private Source**
   Harrison (PI) 08/2007-4/2009
   A phase III, modified single-blind, randomized, parallel-group, comparative, multicenter trial to evaluate the safety, immunogenicity, and non-interference of pediatric vaccines administered concomitantly with Menactra® (Meningococcal [Groups A, C, Y and W-135] polysaccharide diphtheroid toxoid conjugate vaccine) to healthy toddlers.
   Role: Co-Investigator

2. **Private Source**
   Harrison (PI) 03/2007-8/2009
   A Phase 1, Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin (FK463) in Infants and Toddlers (≥ 4 Months to < 24 Months of Age) with Esophageal Candidiasis or Other Invasive Candidiasis.
   Role: Co-Investigator
BIOGRAPHICAL SKETCH

NAME
Lisa Saiman

POSITION TITLE
Professor of Clinical Pediatrics

EDUCATION/ TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR(s)</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Cornell University, New York, NY</td>
<td>BA</td>
<td>1971</td>
<td>English</td>
</tr>
<tr>
<td>Albert Einstein College of Medicine, New York, NY</td>
<td>MD</td>
<td>1983</td>
<td>Medicine</td>
</tr>
<tr>
<td>Columbia University School of Public Health, New York, NY</td>
<td>MPH</td>
<td>1999</td>
<td>Epidemiology</td>
</tr>
</tbody>
</table>

A. Personal Statement

I have been the hospital epidemiologist at Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center since 1992. I have been actively involved in clinical research in the neonatal intensive care unit (NICU) population for 18 years including participation in multicenter observational trials similar to the study proposed. My research interests have focused on outbreak investigations, the use of molecular epidemiology, analysis of risk factors for late onset sepsis and candidemia, and prevention of infections in this vulnerable populations. In addition to local efforts to reduce central line associated bloodstream infections (CLABSIs) in our NICU which as included co-authoring line insertion and line maintenance policies and procedures, I have been actively involved in several multi-site collaborative efforts to reduce bloodstream infections including a New York State collaborative effort aimed at consistent adoption of bundle strategies to reduce CLABSIs in all level III NICUs in the state (see reference 14 below). NYS has had mandatory reporting of central line associated bloodstream infections in all ICUs, including NICUs, since 2008 and I have been a member of the NYS Technical Advisory Panel which advises the NYS Health Department on mandatory reporting strategies.

B. Positions and Honors

1983-1984 Intern, Babies Hospital, Columbia Presbyterian Medical Center, New York, NY
1984-1986 Resident, Babies Hospital, Columbia Presbyterian Medical Center, New York, NY
1986-1989 Fellow, Pediatric Infectious Diseases, Columbia University, New York, NY
1989-1996 Assistant Professor of Pediatrics, Columbia University, New York, NY
1992-Pres Hospital Epidemiologist, Children's Hospital of New York, NY-Presbyterian Hospital
1996-2003 Associate Professor of Clinical Pediatrics, Columbia University, New York, NY
2003-Present Professor of Clinical Pediatrics, Columbia University, New York, NY

Federal Advisory Committees

2007 CDC Epidemiologic, Surveillance, and Laboratory Issues for Nontuberculous Mycobacteria
2007 CDC Public Health Action Plan to Combat Antimicrobial Resistance
2009 CDC In-patient Antimicrobial Use and Stewardship

C. Peer-Reviewed Publications


C. Research Support
Ongoing Research Support
R01 NR010821 Saiman (PI) 7/24/08-4/30/2013
National Institute of Nursing Research (NINR)
Improving Antimicrobial Prescribing Practices in the Neonatal Intensive Care Unit
To measure the impact of interdisciplinary interventions to improve antibiotic prescribing on inappropriate antimicrobial use and antibiotic resistance.

R01 CI000537 Saiman (PI) 9/30/2007-9/29/2010
National Center for Infectious Diseases (NDID)
Applied Research in Antimicrobial Resistance: Studies of Susceptibility Testing
To determine strategies to improve therapy of infection caused by multidrug-resistant Gram-negative bacteria.

UWASH sub award Saiman (PI)
Polymyxin-resistant Pseudomonas in CF Lung Infection
To develop reliable and reproducible \textit{in vitro} susceptibility testing for multidrug-resistant \textit{P. aeruginosa}.

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
</table>

A double blind randomized placebo controlled multinational trial to determine the safety and efficacy of azithromycin in patients with CF 6-18 years of age uninfected with \textit{P. aeruginosa}.

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univ of N. Carolina at Chapel Hill / Muhlebach (PI)</td>
<td></td>
<td>7/1/08 – 6/30/2011</td>
</tr>
</tbody>
</table>

Characterization and Impact of MRSA infection/colonization in CF
Observational and microbiologic study of the epidemiology and clinical impact of different clones of Methicillin-resistant \textit{S. aureus} in patients with CF

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>T32 AI 007531</td>
<td>Saiman (PI)</td>
<td>9/1/09-6/31/14</td>
</tr>
</tbody>
</table>

Training Grant in Pediatric Infectious Diseases
NIH NIAID
The major goals of this project are to prepare physician-scientists with prior clinical training in pediatrics to become academic infectious disease physicians in medical school environments where they will perform research, teach and care for patients.

### Completed Research Support

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral Center for Multiply Resistant Pathogens</td>
<td>Saiman (PI)</td>
<td>7/1/1993-12/31/2009</td>
</tr>
</tbody>
</table>

To perform antimicrobial susceptibility and synergy studies using antibiotic combinations for multi-drug resistant pathogens isolated from patients with cystic fibrosis.

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barriers to Implementation of Infection Control Guidelines for Cystic Fibrosis</td>
<td>Saiman (PI)</td>
<td>4/1/2003-12/31/2009</td>
</tr>
</tbody>
</table>

To assess practices for infection control and microbiology laboratories in the U.S. and to study potential barriers to implementation of infection control guidelines.

<table>
<thead>
<tr>
<th>Source</th>
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<th>Start/End Date</th>
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<tbody>
<tr>
<td>P20 RR020616</td>
<td>Larson(PI)</td>
<td>2004-2007</td>
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</table>

Interdisciplinary Research to Reduce on Antimicrobial Resistance
Saiman (Co-I)
To develop team of interdisciplinary researchers to conduct studies to reduce antimicrobial resistance

<table>
<thead>
<tr>
<th>Source</th>
<th>Proposal PI</th>
<th>Start/End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology, diagnosis and treatment of Mycobacterial Infections</td>
<td>Saiman (PI)</td>
<td>2005-2007</td>
</tr>
</tbody>
</table>

To serve as the mentor to Dr. Marc Foca to perform epidemiology and clinical studies in mycobacterial infections.
BIOGRAPHICAL SKETCH

NAME
P. Brian Smith

POSITION TITLE
Assistant Professor Pediatrics

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
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</thead>
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<tr>
<td>Georgia Institute of Technology, Atlanta, GA</td>
<td>BS</td>
<td>06/97</td>
<td>Chemistry</td>
</tr>
<tr>
<td>Mercer University School of Medicine, Macon, GA</td>
<td>MD</td>
<td>06/01</td>
<td>Medicine</td>
</tr>
<tr>
<td>Duke University, Dept of Pediatrics, Durham, NC</td>
<td>Residency</td>
<td>06/04</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>Duke University, Durham, NC</td>
<td>MHS</td>
<td>06/06</td>
<td>Clinical Research</td>
</tr>
<tr>
<td>Duke University, Dept of Pediatrics, Durham, NC</td>
<td>Fellowship</td>
<td>06/07</td>
<td>Neonatology</td>
</tr>
<tr>
<td>University of North Carolina, Chapel Hill, NC</td>
<td>MPH</td>
<td>06/09</td>
<td>Biostatistics</td>
</tr>
</tbody>
</table>

A. Personal Statement
As a result of my training in both neonatology and biostatistics, I have a broad experience with which to contribute to this project. My areas of research interest include the epidemiology of nosocomial infections and safety and dosing of therapeutic agents in children. I am the recipient of an NICHD funded mentored project examining the pharmacokinetics of antimicrobials in high risk infants (NIH-1K23HD060040-01). I obtained a MHS in Clinical Research from Duke University in 2006 and MPH in Biostatistics at the UNC-Chapel Hill in 2009. I have analyzed data for multiple projects across the Department of Pediatrics (cardiology, neonatology, pediatric intensive care, hematology, endocrinology, neurology, allergy/immunology). I am currently Assistant Professor Pediatrics at Duke University Medical Center with appointments in both the Division of Neonatal-Perinatal Medicine and the Division of Quantitative Sciences. I have been appointed as a Senior Pediatric Consultant to the Office of Pediatric Therapeutics at the US Food and Drug Administration (2006-current). Through both didactic training and clinical research experience, I have developed the skill set necessary to accomplish the tasks outlined in this proposal.

B. Positions and Honors

Positions and Employment
2004-2006: Research Fellow, Department of Molecular Genetics and Microbiology, Duke University
2004-2007: Research Fellow, Duke Clinical Research Institute, Durham, NC
2008-present: Food and Drug Administration, Senior Pediatric Consultant to the Office of the Commissioner, Rockville, MD
2007-present: Assistant Professor, Division of Neonatal-Perinatal Medicine, Duke University, Durham, NC
2007-present: Assistant Professor, Division of Quantitative Sciences, Duke University, Durham, NC
2007-present: Assistant Professor, Duke Clinical Research Institute, Durham, NC

Other Experience and Professional Memberships
2004-present: Member, American Board of Pediatrics (General Pediatrics)
2008-present: Member, American Board of Pediatrics (Neonatal-Perinatal Medicine)
2008-present: Member, North Carolina Pediatric Society
2008-present: Member, Society for Pediatric Research
2008-present: Member, Clinical and Translational Science Awards Pediatric Oversight Committee
2008-present: Member, American Academy of Pediatrics
2009-present: Member, Best Pharmaceuticals for Children Act - Cough and Cold Therapeutic Working Group
2009-present: Member, American Academy of Pediatrics, Section on Clinical Pharmacology and Therapeutics

Honors
1993-1997: Presidential Scholar, Georgia Institute of Technology
2001: Outstanding Pediatric Student, Mercer University School of Medicine
2001: Basic Medical Sciences Award, Mercer University School of Medicine
2001: Physician’s Physician Award, Mercer University School of Medicine
C. Selected Peer-reviewed Publications (from 50 peer-reviewed articles; trainees underlined)

Most relevant to the current application


5. Smith PB, Benjamin DK Jr., Cotten CM, Schultz ED, Guo R, Nowell L, Smithwick ML, Thornburg CD, Is PIC Dwell Time Associated with Increased Infection Risk in Infants?. *Infection Control and Hospital Epidemiology*, August 2008; 29 (8), 749-753. 2768571


9. ACCEPTED

Additional recent publications of importance to the field


D. Research Support

**Ongoing Research Support**

1K23HD060040-01 Smith (PI) 1/15/09-12/31/13

Antimicrobial PK in High Risk Infants

The goal of this Mentored-Patient Oriented Research Career proposal will provide for a structured environment with expert mentorship while studying the PK of meropenem and cefazolin in infants.

Role: PI

HHSN2672007000510 Benjamin (PI) 9/28/07-9/27/10

Best Pharmaceutical for Children Act (BPCA): Use of Meropenem in Infants

This multicenter study will evaluate the safety, tolerability and PK-PD of meropenem in infants <91 days of age with complicated intra-abdominal infections.

Role: Co-Investigator

1R01 HD057956 01 Benjamin (PI) 6/20/08-5/31/13

Prevention of Invasive Candidiasis: PK, Safety, and Neurodevelopmental Outcomes

This multicenter study will determine the safety, efficacy, and pharmacokinetics in the prevention of invasive candidiasis of fluconazole among neonates with a birth weight < 750 g.

Role: Co-Investigator

**Private Source**

Smith (PI) 7/1/09-3/1/10

An open label study to describe the pharmacokinetics of anidulafungin in infants

This single center study will evaluate the safety and PK of anidulafungin in infants < 2 years of age.

Role: PI

**Private Source**

Smith (PI) 3/1/08-2/28/10

This trial will measure the SNO Hgb levels in preterm infants receiving blood transfusions and record tissue oximetry pre and post transfusion.

Role: PI

**Completed Support:**

T32-AI052080 Mitchell (PI) 7/1/04-6/30/06

Molecular Mycology and Pathogenesis Training Program

Evaluate the use of PCR as a diagnostic tool for neonatal candidiasis.

Role: Research Fellow

T32 HD-043728-01A2 Goldberg (PI) 7/1/06-6/30/07

Multidisciplinary Neonatal Training Grant

Clinical research in the area of nosocomial infections

Role: Research fellow

5U01 AI 066590 03 Sub#5 P3030451 Mitchell (PI) 7/1/05-6/30/08

Microfluidic PCR Platform to Detect Microbial DNA

Develop a real-time PCR for the detection of candidemia and community-acquired pneumonia due to *Mycoplasma pneumoniae*.

Role: Co-Investigator

**Private Source**

Smith (PI) 8/24/07-8/24/08

A Phase 1 Open-Label Study of the Safety and Pharmacokinetics of Repeated-Dose Micafungin in Neonates
Investigate the PK and safety of micafungin in infants <120 days of age with sepsis.
Role: PI

1UL 1RR024128-01 Califf (PI) 9/30/06-11/30/08
Duke CTSI (DTMI)
The Duke Clinical and Translational Science Institute will link with other key programs to create a comprehensive home for clinical and translational researchers.
Role: Co-Investigator

5U10 HD045962 05 Benjamin (PI) 3/8/04-12/31/09
The North Carolina Collaborative PPRU Network will increase the availability of pediatric pharmacokinetic data in children.
Role: Co-Investigator
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.**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SONG, XIAOYAN</td>
<td>Assistant Professor of Pediatrics</td>
</tr>
<tr>
<td></td>
<td>Associate Director of Hospital Epidemiology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eRA COMMONS USER NAME</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>eRA Commons User Name</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTITUTION AND LOCATION</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Tongji Medical University, Wuhan, China</td>
</tr>
<tr>
<td>Shanghai Medical University, Shanghai, China</td>
</tr>
<tr>
<td>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD</td>
</tr>
</tbody>
</table>

A. PERSONAL STATEMENT:
I have worked in the field of Hospital Epidemiology and Infection Control for more than 10 years. I have profound experience in designing and conducting epidemiological studies on healthcare associated infections including central line associated bloodstream infections (CLABSI). In my current role as Hospital Epidemiologist at Children’s National Medical Center, I have worked closely with frontline healthcare workers to implement preventive strategies for CLABSI in the NICU in our hospital. Although significant progress has been made toward the eradication of CLABSI, we feel strongly more evidence is needed to construct effective intervention strategies geared for NICU babies, one of the most vulnerable patient populations in hospitalized patients. I’m enthusiastic to join this collaboration. Furthermore, Dr. Millstone and I have had long-standing collaborations before this study opportunity.

B. POSITIONS AND HONORS:
1992 – 1994 Lecturer, Department of Preventive Medicine, Taishan Medical College, Shandong, China
1999 – 2005 Programmer Analyst – EPI, Department of Hospital Epidemiology and Infection Control, Office of Antibiotic Management Program, The Johns Hopkins Hospital, Baltimore, MD
2005 – 2007 Assistant Professor of Medicine, Department of Medicine, Johns Hopkins University
2007 – Present Assistant Professor of Pediatrics, George Washington University Medical Institutes Associate Director of Hospital Epidemiology, Children’s National Medical Center

C. PEER-REVIEWED PUBLICATIONS:


D. Research Support:

1) Title of Grant: Incidence, Mode of Transmission, and Sequelae of Community-Acquired Methicillin Resistant Staphylococcus aureus Infection in the Neonatal Intensive Care Unit and the Effectiveness of Decolonization
   Funding Agency: National Institute of Health
   Dates of Award: 10/1/2010 – 9/30/2012
   Role: Co-PI

2) Title of Grant: Impact of Daily Bathing with Chlorhexidine Impregnated Cloths on Nosocomial Infections in the Pediatric & Cardiac Intensive Care Unit (IND 77954)
   Funding Agency: Private Source
   Dates of Award: 09/30/2007-06/30/2009
   Role: Site PI

3) Title of Grant: Prevention and Outcomes of Hospital Acquired Infections - Prevention Epicenters Program (UR3/CCU31509206)
   Funding Agency: Centers for Disease Control and Prevention
   Dates of Award: 09/30/1997-01/31/2006
   Role: Programmer Analyst

4) Title of Grant: Developing and Optimizing a National Bioterrorism Syndromic Surveillance System (SSS) (1 R01 CI000098)
   Funding Agency: Centers for Disease Control and Prevention
   Dates of Award: 09/15/2003-09/14/2006
Role: Co-PI

5) Title of Grant: Bringing Value through BioSense: a performance-based approach (CDC-RFA-HK06-602)
Funding Agency: Centers for Disease Control and Prevention
Role: Co-PI
**PHS 398 Cover Page Supplement**

1. **Project Director / Principal Investigator (PD/PI)**
   - **Prefix:**
   - **First Name:** Aaron
   - **Middle Name:**
   - **Last Name:** Milestone
   - **Suffix:**

2. **Human Subjects**
   - **Clinical Trial?**
     - No
     - Yes
   - **Agency-Defined Phase III Clinical Trial?**
     - No
     - Yes

3. **Applicant Organization Contact**
   - **Person to be contacted on matters involving this application**
     - **Prefix:**
     - **First Name:** Marissa
     - **Middle Name:**
     - **Last Name:** Flo Roda
     - **Suffix:**
     - **Phone Number:** 4106140257
     - **Fax Number:** 4105027832
     - **Email:** mpiorodi@jhu.edu

   - **Title:** Grants Associate

   - **Street1:** 733 North Broadway, BRB 117
   - **Street2:**
   - **City:** Baltimore
   - **County/Parish:**
   - **State:** MD, Maryland
   - **Province:**
   - **Country:** USA, United States
   - **Zip / Postal Code:** 21287
4. Human Embryonic Stem Cells

* Does the proposed project involve 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/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):  ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.
**PHS 398 Modular Budget, Periods 1 and 2**

**Budget Period: 1**
- **Start Date:** 12/01/2010
- **End Date:** 11/30/2011

**A. Direct Costs**
- *Funds Requested (§):*
  - Direct Cost less Consortium F&A: 50,000.00
  - Consortium F&A: 20,051.00
  - **Total Direct Costs:** 70,051.00

**B. Indirect Costs**

<table>
<thead>
<tr>
<th>Indirect Cost Type</th>
<th>Indirect Cost Rate (%)</th>
<th>Indirect Cost Base ($)</th>
<th>*Funds Requested ($)</th>
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<tbody>
<tr>
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<td>70,850.46</td>
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<tr>
<td>3.</td>
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<td>4.</td>
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</table>

**Cognizant Agency (Agency Name, POC Name and Phone Number):**
US Department of Health and Human Services, Arif Karim (202) 401-2809

**Indirect Cost Rate Agreement Date:** 04/10/2009

**Total Indirect Costs:** 45,344.29

**C. Total Direct and Indirect Costs (A + B)**

- **Funds Requested ($):** 114,195.29

---

**Budget Period: 2**
- **Start Date:** 12/01/2011
- **End Date:** 11/30/2012

**A. Direct Costs**
- *Funds Requested (§):*
  - Direct Cost less Consortium F&A: 50,000.00
  - Consortium F&A: 13,931.00
  - **Total Direct Costs:** 63,931.00

**B. Indirect Costs**

<table>
<thead>
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<th>Indirect Cost Type</th>
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<tr>
<td>1. MTDC</td>
<td>54%</td>
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**Cognizant Agency (Agency Name, POC Name and Phone Number):**
US Department of Health and Human Services, Arif Karim (202) 401-2809

**Indirect Cost Rate Agreement Date:** 04/10/2009

**Total Indirect Costs:** 40,659.71

**C. Total Direct and Indirect Costs (A + B)**

- **Funds Requested ($):** 104,190.71
# PHS 398 Modular Budget, Periods 3 and 4

## Budget Period: 3

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<tr>
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<th>End Date</th>
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</table>

### A. Direct Costs

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<tr>
<th>* Funds Requested ($)</th>
<th>* Direct Cost less Consortium F&amp;A</th>
<th>Consortium F&amp;A</th>
<th>* Total Direct Costs</th>
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### B. Indirect Costs

<table>
<thead>
<tr>
<th>Indirect Cost Type</th>
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<th>Indirect Cost Base ($)</th>
<th>* Funds Requested ($)</th>
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<tbody>
<tr>
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Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

### C. Total Direct and Indirect Costs (A + B)

<table>
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<tr>
<th>Funds Requested ($)</th>
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## Budget Period: 4

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<tr>
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<th>End Date</th>
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### A. Direct Costs

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<th>* Funds Requested ($)</th>
<th>* Direct Cost less Consortium F&amp;A</th>
<th>Consortium F&amp;A</th>
<th>* Total Direct Costs</th>
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### B. Indirect Costs

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<tr>
<th>Indirect Cost Type</th>
<th>Indirect Cost Rate (%)</th>
<th>Indirect Cost Base ($)</th>
<th>* Funds Requested ($)</th>
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<tbody>
<tr>
<td>1.</td>
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Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

### C. Total Direct and Indirect Costs (A + B)

<table>
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<tr>
<th>Funds Requested ($)</th>
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</table>
# PHS 398 Modular Budget, Periods 5 and Cumulative

## Budget Period: 5

<table>
<thead>
<tr>
<th>Start Date:</th>
<th>End Date:</th>
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</table>

### A. Direct Costs

<table>
<thead>
<tr>
<th>* Funds Requested ($)</th>
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<tbody>
<tr>
<td>Direct Cost less Consortium F&amp;A</td>
</tr>
<tr>
<td>Consortium F&amp;A</td>
</tr>
<tr>
<td>Total Direct Costs</td>
</tr>
</tbody>
</table>

### B. Indirect Costs

<table>
<thead>
<tr>
<th>Indirect Cost Type</th>
<th>Indirect Cost Rate (%)</th>
<th>Indirect Cost Base ($)</th>
<th>* Funds Requested ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<td>4.</td>
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Cognizant Agency (Agency Name, POC Name and Phone Number)

<table>
<thead>
<tr>
<th>Indirect Cost Rate Agreement Date</th>
<th>Total Indirect Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

### C. Total Direct and Indirect Costs (A + B)

<table>
<thead>
<tr>
<th>Funds Requested ($)</th>
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</thead>
</table>

## Cumulative Budget Information

### 1. Total Costs, Entire Project Period

- *Section A, Total Direct Cost less Consortium F&A for Entire Project Period*
  
  | $ | 100,000.00 |

- *Section A, Total Consortium F&A for Entire Project Period*
  
  | $ | 34,302.00 |

- *Section A, Total Direct Costs for Entire Project Period*
  
  | $ | 234,302.00 |

- *Section B, Total Indirect Costs for Entire Project Period*
  
  | $ | 86,004.00 |

- *Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period*
  
  | $ | 320,306.00 |

### 2. Budget Justifications

- Personnel Justification
  
- Consortium Justification
  
- Additional Narrative Justification
Personnel Justification:

Aaron M. Milstone, M.D., M.H.S. (Pl, 12 months, no salary support). Dr. Milstone is an Assistant Professor in the Department of Pediatrics, Johns Hopkins University School of Medicine, Division of Infectious Diseases. He has significant experience in clinical research on the prevention of healthcare-associated infections in hospitalized children and in leading multicenter studies. He will be responsible for conducting this research and ensuring the integrity of the work. He will oversee data coordination and analysis and will prepare the results for presentation and publication.

Kathleen Speck MPH (Research coordinator, 12 months). Ms. Speck is a highly experienced research coordinator who has worked with Dr. Milstone to coordinate other multicenter studies. She will assist in coordinating data collection and management.

Research Assistant TBN (2.4 months Year 1, 4.2 months Year 2): The research assistant will be hired to assist with database development and management, cleaning and validating data, as well as to assist with the logistics of the research proposal.
**Consortium/Contractual Justification**

As described in the consortium section of the Research Plan, JHU will be the coordinating center for the seven clinic sites, which are all located in the U.S.

<table>
<thead>
<tr>
<th>Site PI</th>
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# PHS 398 Research Plan

## 1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

- [X] New
- [ ] Resubmission
- [ ] Renewal
- [ ] Continuation
- [ ] Revision

## 2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

<table>
<thead>
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<td>(for Resubmission or Revision only)</td>
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<tr>
<td>2. Specific Aims</td>
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<td>3. Research Strategy</td>
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<td>4. Inclusion Enrollment Report</td>
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<td>5. Progress Report/Publication List</td>
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### Human Subjects Sections

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<td>7. Inclusion of Women and Minorities</td>
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### Other Research Plan Sections

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SPECIFIC AIMS

The long-term objective of this research is to further develop evidence-based strategies to prevent central-line associated bloodstream infections (CLA-BSI) among infants hospitalized in the neonatal intensive care unit (NICU). This proposal builds a multicenter pediatric collaborative to examine the association between catheter dwell time and CLA-BSI in this unique population.

Intravenous (IV) access is essential to provide fluids, medications and nutrition to hospitalized neonates. Since the 1980s, peripherally inserted central venous catheters (PICC) have been increasingly used to provide IV access. PICCs can be placed at the bedside without general anesthesia and can remain in place for days or weeks with seemingly minimal mechanical complications. However, complications do occur, including CLA-BSI, phlebitis, cellulitis, and thrombosis. CLA-BSI have an attributable cost of $10,000 per episode and an associated mortality of up to 20%.

Many studies have shown that the longer a catheter remains in the place, the greater the risk of complication. However, healthcare providers assume that the risk of a complication is constant from day to day, believing that a child with a PICC that has been in place for 50 days has the same risk of having a CLA-BSI as a child with a PICC that has been in place for 20 days.

We recently studied a large population of children in the NICU with PICCs at The Johns Hopkins Hospital. We found that patients with a PICC in place for more than 35 days had a risk profile substantially different from those with a PICC in place for less than 35 days. In those with PICC for more than 35 days, the risk of infection increased by 33% per additional day the catheter was in place. These findings are plausible, because biofilm formation and catheter colonization are thought to contribute to CLA-BSI, and both are associated with increased catheter dwell time. These data challenge the assumption that the daily risk of PICC-associated CLA-BSI is constant. Furthermore, these data call into question the common practice of keeping PICCs in place until signs or symptoms of complications necessitate their removal. We recognize that our single center study does not provide sufficient evidence to support a broad practice change, and therefore we propose to partner with other institutions to conduct a multi-center cohort study with participation of a diverse group of NICUs. Confirming our finding in a larger population will either influence a practice change or will lay the scientific and collaborative foundation for a definitive prospective study.

Hypotheses: The daily risk of PICC-associated CLA-BSI in children hospitalized in the NICU is not constant. Approximately one month after PICC insertion, a threshold exists beyond which time the daily risk of CLA-BSI significantly increases.

Specific Aim. To determine if the risk of PICC-associated CLA-BSI is constant over catheter dwell time, and to identify a threshold beyond which the daily risk of CLA-BSI significantly increases.

We will perform a multicenter retrospective cohort study to collect and characterize data from seven tertiary care NICUs. We will evaluate risk factors for PICC-associated CLA-BSI, focusing on catheter dwell time as a non-linear independent predictor of CLA-BSI.

Significance: PICCs are essential to the care of hospitalized neonates, but CLA-BSI have significant mortality and associated financial costs. Neonates may face unnecessary risk from prolonged PICC dwell time if the risk of CLA-BSI over time is not constant. Current methods for reducing risks from long term catheters, such as using antibiotic impregnated catheters, are often not FDA approved or available for this age group. As PICCs continue to be used widely in other healthcare settings and populations, findings from this collaborative project should stimulate additional studies to improve quality of care and prevent healthcare-associated infections. Our long-term goal is to provide evidence-based justification for instituting preventive measures which could save lives and reduce healthcare costs.
A. Significance:

Long term intravenous access is essential to provide nutrition, fluids, and medications to patients in the NICU. Central line-associated bloodstream infections (CLABSI) can be a devastating complication of central venous catheterization. An estimated 250,000 CLABSI occur in the United States every year, 80,000 of which are in intensive care unit patients.\textsuperscript{13, 14} The attributable mortality of these CLABSIs remains unclear, but recent studies demonstrate a range from 4% to 20%.\textsuperscript{2} CLABSI extends patient length of stay by an average of 7 days, and the attributable cost is $3,700 to $29,000 per infection.\textsuperscript{7, 8, 16-19} Peripherally inserted central venous catheters (PICC) have gained widespread popularity for facilitating vascular access\textsuperscript{20, 21} and comprise the majority of non-umbilical central venous catheters inserted in NICU.\textsuperscript{21} Although PICCs were initially intended for short term vascular access, these catheters often remain in place for prolonged periods of time.\textsuperscript{20, 23}

The Center for Disease Control and Prevention's (CDC) Healthcare Infection Control Practices Advisory Committee (HICPAC) recommends against routine replacement of central venous catheters.\textsuperscript{26} This recommendation is based on two prospective trials in the early 1980s which demonstrated that changing catheters every three or seven days did not reduce infection rates.\textsuperscript{26, 27} These findings led to a dramatic practice change of not routinely replacing catheters. This "no routine replacement" strategy is premised on an assumption that the daily risk of CLABSI is constant over catheter dwell time. Since the mid-1990s, the mean duration of PICC catheterization reported in the literature has been greater than 14 days [see Table 1]. As PICCs have become used more frequently and for greater durations of time, gaps have emerged in our knowledge of the best CLABSI prevention strategies.

Many recent observational studies identified catheter duration as a risk factor for CLABSI\textsuperscript{3-8, 29}, however, evidence for prevention of CLABSI through routine replacement of catheters is lacking.\textsuperscript{30} Most studies that considered catheter duration as a risk factor for CLABSI treated dwell time as a categorical variable to assess risk over the dwell time of the catheter.\textsuperscript{26, 27, 32, 33} Arbitrary cutpoints set at three to seven days following catheter insertion\textsuperscript{26, 27, 32-34} and small sample sizes of 160-234 patients\textsuperscript{26, 32, 33} have limited assessment of prolonged catheter dwell time as a risk factor for CLABSI. PICCs may have a different risk of infection over time compared with tunneled central venous catheters, but most studies focus on all central venous catheters and not exclusively on PICCs. A study by Stenzel and colleagues used a probability density function to demonstrate no relationship between catheter dwell time and the daily probability of developing an infection.\textsuperscript{28} This study is frequently referenced to justify the assumption that risk of infection is constant over time, but 90% of catheters in the cohort were removed by 15 days following insertion, so the author's conclusions were likely underpowered to assess this relationship beyond 15 days.

There are studies which suggest that the daily risk of CLABSI is not constant over time.\textsuperscript{10, 30, 37} Chathas and colleagues studied PICCs in the NICU and found an adjusted relative risk of CLABSI of 8.86 in patients whose PICC dwell time was greater than 21 days compared with those whose PICC dwell time was less than or equal to 21 days.\textsuperscript{10} 83% of CLABSI in that study occurred between 21 and 39 days, and the authors suggested catheters be removed by 4 weeks and replaced if still needed. Our findings, detailed below, from a population of NICU patients with PICCs were similar to those of Chathas.\textsuperscript{20} Other observational studies in adult patients with non-PICC central catheters have suggested that the daily risk of infection is not constant, but no clear threshold can be established from available data.\textsuperscript{30, 37}

This study is significant because, neonates face unnecessary risk from prolonged PICC dwell time if the risk of CLABSI over time is not constant. In the NICU, PICCs are the most common central venous catheter used, and PICC-associated CLABSI can have devastating consequences on fragile neonates. Current methods for reducing risks from long term catheters, such as using antibiotic impregnated catheters, are often not FDA approved or available for this age group. We recognize that our single
center study does not provide sufficient evidence to support a broad practice change, and therefore we propose to partner with other institutions to conduct a multi-center cohort study with participation of a diverse group of NICUs. Findings from this collaborative study will either influence a practice change (for example, identify a threshold beyond catheters are removed or antiseptic locks are instilled) or will lay the scientific and collaborative foundation for a definitive prospective study. Additionally, our findings should stimulate additional studies in other populations to improve quality of care and prevent healthcare-associated infections. This study takes a first step to accomplish our long-term goal to provide evidence-based justification for instituting preventive measures which will save lives and reduce healthcare costs.

B. Innovation

We challenge the assumption that the daily risk of PICC-associated CLA-BSI is constant. We call into question the common practice of keeping PICCs in place until signs or symptoms of complications necessitate their removal. Most studies assessing the relationship between catheter dwell time and CLA-BSI have been limited by their study design. Current statistical approaches enable treating time as a continuous variable to assess the daily risk of CLA-BSI over duration of catheterization. Obtaining data from a large multicenter NICU collaborative will allow us to confirm and generalize our preliminary findings that the risk of CLA-BSI is not constant over PICC dwell time. This proposal will answer a significant gap in the knowledge about CLA-BSI prevention in patients with PICCs and should stimulate discussion and research about the relationship of catheter dwell time and risk of CLA-BSI in other populations with central venous catheters. Below details our findings from a single center study using an innovative statistical approach to test this hypothesis in a manner that has not been done previously.

Patients and Methods: We performed a retrospective cohort study of patients in the Johns Hopkins Hospital NICU who had a PICC inserted between January 1, 2006 and December 31, 2008. For patients with multiple PICC lines placed during their NICU hospitalization, only the first PICC was included. Risk of CLA-BSI over time was assessed by estimating a continuous hazard function and by calculating incidence rates per 10 day intervals from PICC insertion. Both methods identified similar inflection points in the relative risk of CLA-BSI over time. Linear spline terms for modeling days since PICC insertion were introduced into a Poisson regression model to evaluate non-linear changes in the risk of CLA-BSI while adjusting for other variables. We tested various cut-points around the spline terms to assess the robustness of our findings. The final model was chosen on the basis of the Log Likelihood Ratio Test and Akaike’s Information Criterion and confirmed by using Pearson’s Goodness-of-Fit Test.

Results: Six hundred eighty three neonates had PICCs placed during the study period and were eligible for analysis. There were 21 CLA-BSIs within a follow-up time of 10,470 catheter days. The incidence of PICC-associated CLA-BSI over the three year period was 2.01 per thousand catheter days (95% CI=1.24, 3.06). As shown in Figure 1, there appeared to be a non-linear relationship between risk of CLA-BSI and days since PICC insertion. Using Poisson regression analyses, the incidence rate of CLA-BSI increased by 14% per day during the first 18 days following PICC insertion (incidence rate ratio [IRR] 1.14; CI 1.04, 1.25) [see Table 2]. From days 19 through 35 after PICC insertion, the trend reversed (IRR 0.8; 95% CI 0.66, 0.96). From days 36 through 60 after PICC insertion, the incidence rate of CLA-BSI once again increased by 33% per day (IRR 1.33; 95% CI 1.12, 1.57). In univariate and multivariable regression analyses there was no statistically significant association between gestational age groups, birth weight groups, and chronological age groups with the risk of CLA-BSI.

Figure 1. Smoothed Hazard Estimate of CLA-BSI risk over time in NICU patients with PICCs
Conclusion: Our data suggest that catheter duration is an important risk factor for PICC associated CLA-BSI in the NICU. Beyond 35 days from PICC insertion, the daily risk of CLA-BSI increased by a substantial 33% per day. This suggests that there may be We recognize the one study is likely not enough to change current practice. Therefore, we propose to partner with other institutions to validate our finding in a larger population that should either influence a practice change or will lay the scientific and collaborative foundation for a definitive prospective study.

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<th>Table 2: Risk Factors for Central-Line-Associated Blood Stream Infection in Neonatal Intensive Care Unit patients with Peripherally Inserted Central Catheters</th>
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<td><strong>Birth weight category</strong></td>
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<td>&lt;1500 grams</td>
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<tr>
<td>≥1500 grams</td>
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<tr>
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<td>&gt;7 days</td>
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<tr>
<td><strong>Days since PICC Insertion</strong></td>
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<td>&lt; 19 days</td>
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<tr>
<td>19-35 days</td>
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<td>After 35 days</td>
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* represents the change in incidence rate per day within each time interval

C. Approach

Specific Aim. To determine if the risk of PICC-associated CLA-BSI is constant over catheter dwell time, and to identify a threshold beyond which the daily risk of CLA-BSI significantly increases.

Study Design: Retrospective, Multi-center Cohort Study

The hypothesis that there is a non-linear relationship between daily risk of PICC-associated CLA-BSI and time will be tested in a multicenter retrospective cohort study. We will complete a cohort to include neonates hospitalized in the neonatal intensive care unit at one of the participating study hospitals between January 1, 2005 and December 31, 2009. Using this design, we estimate that we will evaluate the outcomes of approximately 5,000 children with PICCs.

This large cohort study design will also allow us to describe the epidemiology of PICC-associated CLA-BSI across institutions. The multicenter design will increase the number of events captured, especially events that occur beyond 35 days of catheterization, increasing our power to detect a difference in the daily risk of CLA-BSI over time. This design is less expensive than a prospective study and will provide the foundation to support a definitive prospective trial.

Study Setting

This study will be initiated and coordinated at Johns Hopkins University (JHU). The principal investigator on this application, Dr. Aaron Milstone, is a member of the Department of Hospital Epidemiology and Infection Control at The Johns Hopkins Hospital and the Division of Pediatric Infectious Diseases. Dr. Milstone has published on the association of catheter duration and risk of CLA-BSI in NICU patients. To assemble a cohort to further test our hypothesis, we will partner with other investigators and sites to ensure adequate numbers of patients and to enhance the generalizability of the study’s findings. The following hospitals (investigators) have agreed to participate in this proposed study: Mayo Eugenio Litta Children's Hospital in Rochester, MN (Dr. W. Charles Huskins), Children's Hospital of Philadelphia, PA (Dr. Susan Coffin), Duke Children's Hospital & Health Center, Durham, NC (Dr. P. Brian Smith), Morgan Stanley Children's Hospital of NewYork-Presbyterian at Columbia University Medical Center in New York City, NY (Dr. Lisa Saiman), Children's National Medical Center in Washington, DC (Dr. Xiaoyan Song), Kosair Children's Hospital in Louisville, KY (Dr. Kristina Bryant), and Children's Mercy Hospital and Clinics in Kansas City, MO (Dr. Robyn Livingston).

Selection of Study Subjects

Children who were hospitalized in the NICU at participating institutions between January 1, 2005 and December 31, 2009 will be eligible for inclusion. Children with a central venous catheter placed while in

Research Strategy
the NICU will be identified by each institution using the electronic medical record or existing databases. Participating institutions were selected because they have central venous catheters days and catheter type documented in the electronic medical record or in existing databases to increase the feasibility of the study. Subjects will be included if they had a PICC inserted during their NICU admission.

Definitions
1. Central venous catheters will be categorized to distinguish PICCs [defined based on their insertion site as a catheter inserted into a peripheral vessel that terminates at or close to the heart or in one of the great vessels] and other central venous catheters [umbilical, tunneled, implantable, and non-tunneled percutaneous (i.e. femoral, internal jugular, subclavian)].
2. PICC follow-up time (PICC dwell time) will be defined as days from line insertion until either 1) date of CLA-BSI, 2) termination of the PICC, or 3) administrative censoring at discharge from NICU.
3. A CLA-BSI will be defined using the surveillance definition established by the Center for Disease Control and Prevention’s National Healthcare Safety Network’s (NHSN).
4. A PICC-associated CLA-BSI will be defined as a CLA-BSI in a patient with a PICC.

Determination of Outcome
The outcome of interest will be PICC-associated CLA-BSI as identified by infection control practitioners. Each participating institution has trained infection control practitioners who perform prospective surveillance to monitor positive cultures in patients with indwelling catheters, using laboratory databases and infection surveillance support systems. The above definitions are applied to determine which patients meet the surveillance definition of a CLA-BSI. The research team on this proposal will not be involved in identifying CLA-BSI. A list of all patients with CLA-BSI during the study period will be obtained from the institution’s infection control group. Charts will be reviewed at random to validate the outcome in patients identified by the institution’s infection control group. Patients with CLA-BSI attributed to a PICC will be included as having the outcome of interest.

Clinical and Demographic Data
Each participating institution has the capacity to query catheter insertion and removal dates in their electronic medical record or existing databases. These dates, catheter type, and catheter location will be collected for all patients during the study period. Each site will perform medical record review on random patients to validate that this electronic data correctly identifies these variables. Data on race, ethnicity, gender, date of birth, date of hospital admission, date of hospital discharge, date of NICU admission, date of NICU discharge, gestational age at birth, birth weight, dates of TPN administration, date of blood culture, and organism cultured will be extracted from hospital databases and medical records.

Data Collection
Prior to any work being performed on this research proposal it will be submitted for review and approval by the Institutional Review Board at JHU and then at each of the participating sites. Site investigators will be responsible for adapting the JHU IRB proposal to meet the requirements of their institution. Upon IRB approval, site investigators will work with the appropriate information systems groups to generate lists of eligible patients.

Each institution will maintain a master list of patients with unique study identifiers. The institutions master list will be password protected and remain with the co-investigator at each institution so only they will have access to their own patients’ unique identifiers. Protected health information that identifies patients will be stripped from all analytic datasets and replaced by a unique study identifier that can be linked back to the patient using the master list at each institution, if deemed necessary. Only de-identified data will be sent to the coordinating center.

Before sending data to the coordinating site, edit checks will be performed for consistency and accuracy of the data. Edit checks will include logical checks, out-of-range checks, missing and completeness checks. Any discrepancies found by this validation process will be queried to the data source for clarification. Resolved queries will be incorporated into the database. Another source of checking will result from the statistical description of the data (such as identifying outliers) and will be
reported. Once entry, review, and resolution have been completed for all subjects, the database will be considered closed.

**Statistical Analysis**

**Overview**

The goal of this retrospective cohort study is to determine if the risk of PICC-associated CLA-BSI is constant over catheter dwell time and whether a threshold exists beyond which daily risk of CLA-BSI significantly increases.

**Descriptive Analysis**

We will first perform descriptive analyses to characterize the patient populations at each institution and the combined cohort by reporting of means, standard deviations, medians, and ranges for all measured variables.
Potential Limitations
- Participants can be improperly categorized with regards to exposure or outcome. As mentioned above, we will perform random validation to ensure classification of catheter type. Given the cumulative experience of infection control professionals, we will not reclassify CLA-BSI. These events undergo tremendous scrutiny in the era of mandatory public reporting of CLA-BSI, so we are confident that CAL-BSIs are appropriately classified.
- Data will be limited to those contained in the hospital records. Patients can leave the NICU with a PICC still in place and an event that occurs following NICU discharge will not be captured. In our previous study we found that more than 90% of children had their PICCs removed before unit discharge, so we anticipate having near complete outcome ascertainment on all patients.
- We will conduct multivariate analyses to control for confounding factors. In any observational study, there is always the potential for residual confounding. We hope that disease severity which we cannot control for in this study may be co-linear with other observed variables that we will control for in the analysis. For example, time in the NICU may correlate with PICC duration and this might be confounded by disease severity. Older children stay in the NICU longer if they are sicker, but all extremely premature infants have prolonged NICU hospitalizations. By controlling for gestational age and chronologic age at time of PICC placement, we may be indirectly controlling for disease severity.

Proposed Timeline

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<td>Database development</td>
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<tr>
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Summary, potential impact, and future studies
PICCs are essential to the care of hospitalized neonates, but CLA-BSI have significant mortality and associated financial costs. We hope to confirm earlier findings that the risk of CLA-BSI is not constant over PICC duration and a threshold exists beyond which time PICC replacement should be considered to reduce the incidence of PICC-associated CLA-BSI. Assembling data from multiple centers will enhance the generalizability of the study’s findings and make a compelling case to consider revising national guidelines regarding routine replacement of PICCs in select populations. Our data will suggest a threshold at which preventive catheter replacement would offer maximum reduction in PICC-associated CLA-BSI, but further studies will be needed to identify an acceptable threshold for catheter replacement beyond which absolute risk reduction would outweigh costs associated with catheter replacement. This data will lay the foundation for a definitive prospective study and similar studies in other populations of patients with PICCs. This study will further the evidence-based CLA-BSI prevention measures which can save lives and reduce healthcare costs.
Protection of Human Subjects

1. Risk to the Subjects

**Human Subjects Involvement and Characteristics**

The proposed research consists of a multicenter retrospective cohort study. As outlined in the proposal, the eligible study population will consist of all patients hospitalized in the NICU at participating institutions between January 1, 2005 and December 31, 2009. Children hospitalized in the participating NICUs are a heterogeneous group broadly representing various genders, races and ethnicities. We anticipate enrolling approximately 4,000 patients in the study who had a PICC during their NICU admission. We will use only data that are already in existence as a result of routine clinical care, subjects will not be contacted by members of the study team, and no further information or participation is requested of subjects.

**Sources of Materials**

For the proposed study, we will use only data that are already in existence as a result of routine clinical care, subjects will not be contacted by members of the study team, and no further information is requested of subjects. Each participating institution has the capacity to query catheter insertion and removal dates in their electronic medical record or existing databases. These dates, catheter type, and catheter location will be collected for all patients during the study period. Each site will perform medical record review on random patients to validate that this electronic data correctly identifies these variables. Data on race, ethnicity, gender, date of birth, date of hospital admission, date of hospital discharge, date of NICU admission, date of NICU discharge, gestational age at birth, birth weight, date of blood culture, and organism cultured will be extracted from hospital databases and medical records. The outcome of interest will be PICC-associated CLA-BSI as identified by infection control practitioners.

Each participating institution has trained infection control practitioners who perform prospective surveillance to monitor for the development of bacteremia in patients with indwelling catheters, using laboratory databases and infection surveillance support systems. Definitions are applied to determine which patients meet the surveillance definition of a CLA-BSI. The research team on this proposal will not be involved in identifying CLA-BSI. A list of all patients with CLA-BSI during the study period will be obtained from the institution’s infection control group. Patients with CLA-BSI attributed to a PICC will be included as having the outcome of interest.

Prior to any work being performed on this research proposal it will be submitted for review and approval by the Institutional Review Board at JHU and then at each of the participating sites. Site investigators will be responsible for adapting the JHU IRB proposal to meet the requirements of their institution. Upon IRB approval, site investigators will work with the appropriate information systems groups to generate lists of eligible patients.

Each institution will maintain a master list of patients with unique study identifiers. The institutions master list will be password protected and left with the co-investigator at each institution so only they will have access to their own patients’ unique identifiers. Protected health information that identifies patients will be stripped from all analytic datasets and replaced by a unique study identifier that can be linked back to the patient using the master list at each institution, if deemed necessary. Only de-identified data will be sent to the coordinating center.

Before sending data to the coordinating site, edit checks will be performed for consistency and accuracy of the data. Edit checks will include logical checks, out-of-range checks, missing and completeness checks. Any discrepancies found by this validation process will be queried to the data source for clarification. Resolved queries will be incorporated into the database. Another source of checking will result from the statistical description of the data (such as identifying outliers) and will be reported. Once entry, review, and resolution have been completed for all subjects, the database will be considered closed.

**Potential risks**

This is an observational study and therefore risk, if any, is minimal. One potential risk is the loss of confidentiality imparted by participating in any research study where the patient’s identifying information is available. The potential for loss of confidentiality will be protected as described below.

2. Adequacy of protection against risks

**Recruitment and Informed Consent**

Protection of Human Subjects
Given that the proposed research will be conducted using only existing sources of data, we will seek a waiver of the requirement for informed consent from the Institutional Review Board of the Johns Hopkins University and the IRBs of all participating institutions. The study meets all of the requirements for a waiver of informed consent including the following:

- There is minimal risk to the study subjects (the procedure for minimizing the risk of breaching confidentiality is discussed below);
- The waiver will not adversely affect the rights and welfare of the subjects;
- The research could not feasibly be carried out without the waiver.

**Protection against risk**

We will institute strict procedures to maintain confidentiality. All patients will be assigned a study identification number. Each site will maintain a password protected code key file that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. Only de-identified data will be sent to the coordinating center.

After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed in accordance with local regulations, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained according to hospital operations policy. During the course of the study, information collected will not be disclosed to anyone other than the study personnel. This data and research will not be used or disclosed to any persons or entity outside of the study institution. No sensitive information will be collected.

3. **Potential Benefits of the proposed research**

There is no direct benefit to the study subjects, though we feel that the proposed studies could clearly benefit all patients who require admission to the NICU by providing data on the epidemiology of CLA-BSI and potential for an association between PICC dwell time and the risk of infection.

4. **Importance of the knowledge gained**

Neonates may face unnecessary risk from prolonged PICC dwell times if the risk of CLA-BSI over time is not constant. As PICCs continue to be used widely in other healthcare settings and populations, findings from this collaborative project should stimulate additional studies to improve quality of care. Our long-term goal is to provide evidence-based justification for instituting preventive measures which could save lives and reduce healthcare costs.
Inclusion of Women and Minorities in Clinical Research
These studies use existing data. Recruitment was not based on gender or race, and minorities were included in the study population.
**Targeted/Planned Enrollment Table**

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

**Study Title:**
Catheter Dwell Time and Risk of Bloodstream Infections in Hospitalized Neonates

**Total Planned Enrollment:** 4000

<table>
<thead>
<tr>
<th>TARGETED/PLANNED ENROLLMENT: Number of Subjects</th>
<th>Sex/Gender</th>
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<th></th>
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<tbody>
<tr>
<td>Ethnic Category</td>
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<td>Males</td>
<td>Total</td>
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<td>110</td>
<td>200</td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>1710</td>
<td>2090</td>
<td>3800</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of All Subjects</strong> *</td>
<td>1800</td>
<td>2200</td>
<td>4000</td>
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| Racial Categories                             |      |      |      |
| American Indian/Alaska Native                 | 9    | 11   | 20   |
| Asian                                         | 72   | 88   | 160  |
| Native Hawaiian or Other Pacific Islander     | 9    | 11   | 20   |
| Black or African American                     | 792  | 968  | 1760 |
| White                                         | 828  | 1012 | 1840 |
| **Racial Categories: Total of All Subjects** * | 1800 | 2200 | 4000 |

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."
Inclusion of Children in Clinical Research
Children are focus of this research. However, we will only study children in the neonatal intensive care unit for this study.
Select Agents
Not applicable
References


29. [In press]


Consortium/Contractual Arrangements

Johns Hopkins will act as the coordinating center for this study. Seven institutions have signed agreements to provide data as specified in the proposal to Johns Hopkins. The contractual activities represent a significant proportion of the project, because no single site has enough data to answer the hypothesis being tested. Each institution has been informed and agrees to establish the necessary inter-organizational agreements to complete the proposed study.
Resource Sharing

Not applicable
# PHS 398 Checklist

**1. Application Type:**
From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:
  - [ ] New
  - [ ] Resubmission
  - [ ] Renewal
  - [ ] Continuation
  - [ ] Revision

Federal Identifier: ____________

**2. Change of Investigator / Change of Institution Questions**

- [ ] Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix: ____________

* First Name: ____________

Middle Name: ____________

* Last Name: ____________

Suffix: ____________

- [ ] Change of Grantee Institution

* Name of former institution:

**3. Inventions and Patents  (For renewal applications only)**

* Inventions and Patents: [ ] Yes [ ] No

If the answer is "Yes" then please answer the following:

* Previously Reported: [ ] Yes [ ] No
4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes  ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

<table>
<thead>
<tr>
<th>*Budget Period</th>
<th>*Anticipated Amount ($)</th>
<th>*Source(s)</th>
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5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes  ☐ No