APPLICATION FOR FEDERAL ASSISTANCE

SF 424 R&R

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION

❍Pre-application ●Application ❍Changed/Corrected Application

2. DATE SUBMITTED

Applicant Identifier

4. a. Federal Identifier

b. Agency Routing Identifier

c. Previous Grants.gov Tracking ID

5. APPLICANT INFORMATION **Organizational DUNS:** 092530369

Legal Name: The Regents of the University of California, Los Angeles

Department: Division:

Street1: Office of Contract and Grant Administration Street2: 10889 Wilshire Boulevard, Suite 700

City: Los Angeles County/Parish: Los Angeles County State: CA: California

Province: Country: USA: UNITED STATES ZIP / Postal Code: 90095-1406

Person to be contacted on matters involving this application

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Mr.	Frank		Falcon II	

Position/Title: Grant Analyst

Street1: 10889 Wilshire Boulevard, Suite 700 Street2:

City: Los Angeles County/Parish: Los Angeles County State: CA: California

Province: Country: USA: UNITED STATES ZIP / Postal Code: 90095-1406

Phone Number: 310-206-9898 Fax Number: Email: frank.falcon@research.ucla.edu

6. EMPLOYER IDENTIFICATION NUMBER*(EIN) or (TIN)*: 1-956006143-A1

7. TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ❍Women Owned ❍Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:

●New ❍Resubmission

❍Renewal ❍Continuation ❍Revision

If Revision, mark appropriate box(es).

❍A. Increase Award ❍B. Decrease Award ❍C. Increase Duration

❍D. Decrease Duration ❍E. Other*(specify)*:

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

9. NAME OF FEDERAL AGENCY:

National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Clinical study of STI screening to prevent adverse birth and newborn outcomes

12. PROPOSED PROJECT:

Start Date	Ending Date
09/01/2019	08/31/2024

13. CONGRESSIONAL DISTRICT OF THE APPLICANT:

CA-033

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Dr.	Jeffrey		Klausner	MD

Position/Title: Professor
Organization Name: UCLA David Geffen School of Medicine
Department: Medicine
Division: Infectious Diseases
Street1: 9911 West Pico Blvd
Street2: Suite 955
City: Los Angeles
County/Parish: Los Angeles County
State: CA: California
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 90035-2738
Phone Number: 310-557-3044
Fax Number: 310-557-3679
Email: JDKlausner@mednet.ucla.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	$4,316,456.00
b. Total Non-Federal Funds	$0.00
c. Total Federal & Non-Federal Funds	$4,316,456.00
d. Estimated Program Income	$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. 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. SFLLL or other Explanatory Documentation. File Name: Mime Type:

19. Authorized Representative

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Mr.	Frank		Falcon II	

Position/Title: Grant Analyst
Organization Name: The Regents of the University of California, Los Angeles
Department: Office of Contract & Grant Adm
Division:
Street1: 10889 Wilshire Boulevard, Suite 700
Street2:
City: Los Angeles
County/Parish: Los Angeles County
State: CA: California
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 90095-1406
Phone Number: 310-206-9898
Fax Number:
Email: frank.falcon@research.ucla.edu

Signature of Authorized Representative **Date Signed**

20. Pre-application File Name: Mime Type:

21. Cover Letter Attachment File Name: Cover_letter_large_grant_approval1054050549.pdf Mime Type: application/pdf

UNIVERSITY OF CALIFORNIA, LOS ANGELES

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Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Public Health
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David Geffen School of Medicine
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January 27, 2019

Delmyra Turpin, RN, MPH, CCRP
Sexually Transmitted Infections Branch
DMID/NIAID/NIH/DHHS

RE: PA-19-055 (R01)

Dear Ms. Turpin,

Dr. Medina-Marino and I are very pleased to submit this application for our study, entitled "***Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes.***" We submit this proposal for your consideration as an R01 in NIAID, building upon our current R21 award through NICHD. However, we also think NICHD could be an appropriate Institute for funding.

We very much appreciate your approval for submission of a proposal with a budget greater than $500,000 per year in direct costs. As you know, to be most effective we need to request direct costs ranging from $541,759 - $842,154 each year. Bringing together a team of established investigators from both South Africa and the United States, our team has unique resources and solid expertise in HIV infection, microbiome analysis, molecular epidemiology, and sexually transmitted infection (STI) microbiology, care, and treatment.

This study will be led by two PIs, one from the University of California, Los Angeles (UCLA) and one from the Foundation for Professional Development (FPD) in Pretoria, South Africa. We think our proposed project is an outstanding fit for the R01 mechanism, and are enthusiastic about the potential for our findings to significantly impact STI screening and treatment guidelines for pregnant women living with HIV in low and middle-income countries.

In addition to faculty and staff at UCLA and FPD, this application involves Co-Investigators from the University of Cape Town, the University of Alabama at Birmingham, and Louisiana State University, as well as the expert consultation of an outstanding biostatistician from the University of Mississippi.

We appreciate your consideration of this application and look forward to hearing the results of the review.

Sincerely,

Jeffrey D. Klausner, MD, MPH
UCLA Professor of Medicine and Public Health

Andrew Medina-Marino, PhD
Head, FPD Research Unit

National Institute of Allergy and Infectious Diseases

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892
www.niaid.nih.gov

February 1, 2019

Jeffrey David Klausner, M.D., M.P.H.
Professor of Medicine and Public Health
UCLA Division of Infectious Diseases
10920 Wilshire Blvd
Suite #350
Los Angeles, CA 90024

Re: "Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes"

Dear Dr. Klausner,

This letter notifies you that the National Institute of Allergy and Infectious Diseases will accept assignment of your resubmission application for a Big Grant R01 to the Institute. This agreement is contingent upon resubmission of your application by the **February 5, 2019** receipt date. Special procedures apply because your application will request $500,000 dollars or more in direct costs in one or more years or is part of a multi-project application requesting such an amount. Please note that if, after peer review, your application is not funded, you must obtain NIAID's agreement to submit any resubmission (amended) or renewal application.

You should check that both your personal and institutional registrations in eRA Commons are in place. Institutional registration on Grants.gov must be completed in advance by your authorized business official. Registration can take several weeks.

NIAID policy requires that, in your application submission to the Center for Scientific Review, you include a cover letter documenting NIAID's concurrence to accept assignment of your application. Please use this letter to comply with that policy:

- Name of the institute or center that agreed to accept your application: **NIAID**
- Name of the program staff member who performed required clearances: **Delmyra Turpin, R.N., M.P.H.**
- Receipt date provided by the program officer: **February 5, 2019**
- Earliest Peer Review date: **June 2019**
- Earliest date the NIAID Advisory Council would consider your application for award: **August 2019**
- Earliest anticipated start date: **September 2019**

NIH will return your application to you without review if it does not include documentation that an NIAID program officer has previously agreed the Institute will accept the application.

Furthermore NIAID may not be able to fund your application, even if peer reviewers give it an exceptional priority score. By accepting your application for review, we do not guarantee funds will be available for an award. Funding depends on several factors, including technical merit, relative program priority, and available funds.

You must submit the same application that the program division approved. If you do need to change the application after that approval, talk to your program officer and inform the scientific review officer about the changes.

Please address any questions you may have regarding this information to: Delmyra B. Turpin, R.N., M.P.H., 5601 Fishers Lane, 8E56, Bethesda, MD 20892; Tel. +1 (240) 669-5597; email: Delmyra.Turpin@nih.gov.

Sincerely,

Irene B Glowinski for EE

Emily Erbelding, M.D., M.P.H.
Director, Division of Microbiology and Infectious Diseases
NIAID/NIH

Cc: Delmyra B. Turpin, R.N., M.P.H., Program Officer, ESTIB, DMID
Carolyn Deal, Ph.D., Branch Chief, ESTIB, DMID
Wayne Crum, Chief, Budget & Financial Management Branch, OMIFM
Emily Linde, Program Director, Grants Management Program, DEA

Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: UCLA David Geffen School of Medicine/Infectious Diseases

* Street1: 10920 Wilshire Blvd		Street2: Ste 350
* City: Los Angeles	County: Los Angeles	* State: CA: California
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: 90024-1688
DUNS Number: 092530369	* Project/Performance Site Congressional District: CA-033	

Project/Performance Site Location 1

Organization Name: Foundation for Professional Development

* Street1: 173 Mary Road		Street2: The Willows
* City: Pretoria	County:	* State:
Province:	* Country: ZAF: SOUTH AFRICA	* Zip / Postal Code:
DUNS Number: 568904572	* Project/Performance Site Congressional District: 00-000	

Project/Performance Site Location 2

Organization Name: Lousiana State University Health Sciences Center - NO

* Street1: 533 Bolivar Street		Street2:
* City: New Orleans	County: Orleans	* State: LA: Louisiana
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: 70112-2256
DUNS Number: 782627814	* Project/Performance Site Congressional District: LA-002	

Project/Performance Site Location 3

Organization Name: University of Alabama at Birmingham

* Street1: 1720 2nd Ave South		Street2: ZRB 242
* City: Birmingham	County: Jefferson	* State: AL: Alabama
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: 35294-0009
DUNS Number: 063690705	* Project/Performance Site Congressional District: AL-007	

File Name	Mime Type

Additional Location(s)

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

Exemption Number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If no, is the IRB review Pending? ● Yes ❍ No

IRB Approval Date:

Human Subject Assurance Number 00004642

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 the Project have an Actual or Perceived Impact – positive or negative – 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.a. * Is the research performance site designated, or eligible to be designated, as a historic place? ❍ Yes ● No

5.b. If yes, please explain:

6.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? ● Yes ❍ No

6.b. If yes, identify countries: South Africa

6.c. Optional Explanation:

7. Project Summary/Abstract	project_abstract1054050480.pdf	Mime Type: application/pdf
8. Project Narrative	project_narrative1054050484.pdf	Mime Type: application/pdf
9. Bibliography & References Cited	References_STI_R01_Feb_2019105411 4155.pdf	Mime Type: application/pdf
10. Facilities & Other Resources	Facilities_and_Resources1054050477.pdf	Mime Type: application/pdf
11. Equipment	Equipment_page1054050483.pdf	Mime Type: application/pdf
12. Other Attachments	Foreign_Justification1054050562.pdf	Mime Type: application/pdf

ABSTRACT

Infections with *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) during pregnancy are associated with premature rupture of membranes, preterm labor and delivery, low birth weight, congenital infections, perinatal death and mother-to-child transmission of HIV infection. Sexually transmitted infections (STIs) like these are common in pregnant women globally, but often go undiagnosed; recent work by our group found a 41% STI prevalence amongst HIV-infected pregnant women, of which 64% of infections were asymptomatic. Recent research suggests the vaginal microbiome may play a critical role in STI acquisition, persistence and treatment outcomes. Our pilot work has shown that diagnostic testing for CT, NG, and TV in antenatal care services for HIV-infected pregnant women in South Africa is highly acceptable and feasible; however, our work has made clear that evaluating the impact and cost effectiveness of different diagnostic screening strategies that optimally decrease the burden of STIs during pregnancy and at time-of-delivery is urgently needed. Furthermore, our findings highlight that biological factors that increase the risk for STI persistence and/or treatment failures must be further investigated.

In response to the need to 1) identify optimal, cost-effective screening strategies that decrease the burden of STIs during pregnancy and reduce adverse birth outcomes, 2) provide evidence to update WHO's syndromic management guidelines, and 3) elucidate the role of the vaginal microbiome in STI treatment outcomes, we propose a novel, highly innovative study with the following three Aims:

Aim 1: Evaluate 3 different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and disability-adjusted life-year (DALY) averted.

Aim 3: Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women.

Our proposed 5-year study will enroll 1250 HIV-infected and 1250 uninfected pregnant women from three large ANC clinics in Tshwane District, South Africa, as well as their ~2500 neonates and up to 834 male partners. Our research team, led by established researchers, has significant expertise and experience in all aspects of the proposed study. Our multi-institutional collaborations will allow us to leverage unique implementation platforms and resources, and allow for rapid dissemination of findings to South African and global stakeholders.

PROJECT NARRATIVE

This effectiveness trial will increase understanding of the value and cost-effectiveness of diagnostic screening for sexually transmitted infections (STIs) among pregnant women in low and middle-income countries, to reduce adverse pregnancy and infant outcomes. Further, results from this study will provide important data on the role of the vaginal microbiome in Chlamydia trachomatis (CT) testing outcomes and further rationale for studying the vaginal microbiome in pregnant women with CT treatment failure. Together, findings from this R01 are likely to inform changes to STI screening and treatment guidelines in low-middle income countries globally.

LITERATURE CITED

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FACILITIES AND OTHER RESOURCES

The proposed research will be conducted within the University of California, Los Angeles (UCLA) in Los Angeles, in collaboration with the Foundation for Professional Development (FPD) in Pretoria, South Africa, the University of Alabama at Birmingham (UAB), Louisiana State University (LSU), the University of Cape Town (UCT), The South African Medical Research Council and the Anova Health Institute / University of Pretoria. These organizations have years of experience with successful collaborations with each other, and look forward enthusiastically to combining their critical resources for the first time, for the implementation of this study.

University of California, Los Angeles (UCLA)

Division of Infectious Diseases
The Division of Infectious Diseases, Department of Medicine has a broad and growing portfolio of HIV/STD prevention and policy research, focused primarily on the US and developing country issues, with ongoing NIH-funded research projects in South Africa, Peru, China, Uganda, and Malawi.

Office Space:
Dr. Klausner's research unit occupies approximately 900 sq ft of office space at 10920 Wilshire Blvd, Suite 350, Los Angeles, CA 90024. In addition, he has a designated office space in the Community Health Sciences Building, located on the UCLA campus.

Computers, Telecommunications, IT:
The UCLA personnel named on this project all have computers, printers, telephones, fax, and copying capabilities. The informational technology infrastructure is maintained by the IT group in the UCLA Department of Medicine. UCLA routinely uses Skype and ReadyTalk for international telecommunications.

Administration:
Dr. Chrys Stafylis is the IRB Coordinator and Research Manager. He is supported by the administrative team, including Fund Manager Richard Tristan, within the Division of Infectious Diseases and the UCLA Department of Medicine on all fund, human resources, and grant-related issues.

Foundation for Professional Development (FPD)

FPD was established in 1997 by the South African Medical Association (SAMA). In 2000, FPD became registered as a private institution of higher education. FPD prides itself on being one of a few private higher education institutions in South Africa that fully engages in the three scholarships of higher education- teaching and learning, research and community engagement/capacity development.

Office Space: The FPD office complex, made up of East and West block, is physically located at Struland Office Park, 173 Mary Road, The Willows, Pretoria. FPD's premises occupies approximately 1686m^2 of office space and has offices at the following locations around South Africa.

57 Western Avenue
Vincent
East London, 5247

206 Cape Road
Newton Park
Port Elizabeth, 6000

185 Duxbury Road
Hatfield
Pretoria, 0028

115 Marshal Street
Polokwane
0699

ERF 791
Thohoyandou
Polokwane East, 0699

2a Financial Square
Nelson Mandela Drive
Witbank, 1035

Computers, Telecommunications, IT: The FPD personnel named in the project have access to password-protected computers, printers, telephones, fax and photocopying machines and these are managed by the IT department of FPD. Tele-conference facilities are also available for communication. To address quality control of health information, FPD successfully developed and deployed a tier 3 electronic health information system in 52 facilities that covered 150 000 patient records and developed extensive experience in ensuring data quality in a public sector clinical environment. A data audit in 2011 by the USG reported very high data quality.

Administration: FPD's Finance Department is made up of 18 qualified accountants and bookkeepers and is overseen by the group Chief Financial Officer. Each year, the relevant financial staff undergo US Government Donor and International Financial Reporting Standards (IFRS) training to keep up-to-date with current developments and policies. The strength of FPD's Finance Team is proven by a history of unqualified statutory and donor audit reports. Due to the large number of donor and sponsor grants managed by FPD a state of the art financial management system – ACCPAC's Enterprise Resource Planning system (ERP) – was implemented in 2007 and customized to meet the requirements of reporting to multiple donors on multiple projects and to support decentralized office locations. Customized reporting modules were designed to process and match reporting requirements on large scale donor funded programs in multiple currencies, multiple locations and with multiple donors each requiring unique financial reporting at flexible intervals. This extensive customization includes an internal reporting and budgeting facility to effectively manage the different grants, donors and departments. To date this system has managed and met all reporting requirements for funders such as PEPFAR, the Bill and Melinda Gates Foundation, OFID,NHI, Atlantic Philanthropies, MRC, Department of Health (South African Government) etc. This system is also able to provide accurate and reliable financial statements, forecasting of cash flow and assessment of fund utilization rates and a purchasing system that is web based and controls all purchase orders against appropriate authorization and available funding. FPD is not only responsible for the financial control of its own funds, but performs treasury functions for all of its JV's and subsidiaries, and a number of international NGO's with whom FPD have MOU's to provide this particular function.

University of Alabama at Birmingham (UAB)

Scientific Environment:
The University of Alabama at Birmingham (UAB) Division of Infectious Diseases (ID) and Department of Medicine provide a stimulating intellectual environment with regularly scheduled teaching conferences, journal clubs, research seminars, ID and Medicine Grand Rounds, and visiting speakers in a wide range of specialties. The UAB Center for Clinical and Translational Science (CCTS) provides workshop sessions in areas of clinical trials, epidemiology, biostatistics, ethics, clinical genetics research, behavioral research, outcomes research, dissemination of results, and grant writing and funding opportunities. Additionally, there is a long history of successful STI research studies conducted by the STD Research Group in the ID Division at UAB. Dr. Muzny has been conducting clinical research at the Jefferson County Department of Health (JCDH) STD clinic for the past 8 years. In addition, the UAB School of Public Health (SOPH), located in the Ryals Public Health Building, houses the UAB Department of Biostatistics, for which Dr. Redden is a senior faculty member. The UAB SOPH is in close geographic proximity to the UAB Medical Center by being located 2 blocks down the street, within easy walking distance.

Office Space:
Dr. Muzny's office is located in the Zeigler Research Building (ZRB) on the UAB campus, directly down the hall from the UAB STD Research Laboratories, 1 block from the UAB Personal Health clinic, and 2 blocks from the Ryals Public Health Building. Secretarial support is supplied by the ID Division. A 385 ft2 room adjacent to these offices serves as the UAB STD Program Conference Room for scheduled meetings and presentations. The STD Research Program Data Manager's office is located directly across the hall from Dr. Muzny's office. Dr. Redden's office is located in the Ryals School of Public Health Building. All offices are fully furnished and equipped with phones, network-linked personal computers, fax machines, and copiers.

Computers, Telecommunications, IT:
Dr. Muzny has SAS v9.4, Windows Office, and EndNote installed on her computer. **Dr. Redden**, Dr. Redden, as faculty of the UAB Biostatistics Department, has access to a wide array of statistical and 'omics' software,

personal desktops and laptop computers, and access to distributed high-performance computing (HPC) cluster solutions. Regarding HPC, UAB Information Technology (IT) Research Computing maintains high performance compute and storage resources for investigators. The Cheaha compute cluster provides 3,120 conventional CPU cores across five generations of hardware that provide over 120 TFLOP/s of combined computational performance, and 20 TB of system memory interconnected via an Infiniband network. A high-performance, 6.6PB raw GPFS storage on DDN SFA12KX hardware and 180TB Lustre parallel file system built on a Direct Data Network (DDN) hardware platform is also connected to these cores via the Infiniband fabric. An additional 20TB of traditional SAN storage and 432TB of OpenStack+Ceph storage is available via a 10+ GigE network fabric. This general access compute fabric is available to all UAB investigators. Cheaha is a general-purpose computer resource made available to the UAB community by UAB IT. As such, it is available for legitimate research and educational needs and is governed by UAB's Acceptable Use Policy (AUP) for computer resources. Dr. Redden has access to a wide range of statistical software including Microsoft products as well as SAS, S-plus, SPSS, and R. His department also maintains additional, more specialized software programs. For software development purposes, his group has access to compilers for Fortran, C/C++, Perl, and Java as well as Fortran and Java IMSL libraries. In addition, in 2012, UAB negotiated a campus-wide Matlab license with investigator access to over two dozen toolboxes, including the Statistics, Bioinformatics, Optimization, Symbolic Math, and Parallel Computing toolboxes. To facilitate collaborative software development, tools like Subversion (Source Code Management System), Confluence Wiki (Content Management System), and JIRA (Project Management Tool) can be employed from the intranet resource pool.

Laboratory Resources:

The UAB STD Research Program laboratories are located on the 2nd floor of Tinsley Harrison Tower (THT 230, 234), Zeigler Research Building (ZRB 203, 205, 207, 209, 215, 221, 223, 224, 231, 233, 235, 238), and Lyons Harrison Research Building (LHRB 338, 340, 342, 344, 347,348, 350). This contiguous research and CAP/CLIA accredited lab space occupies over 6,000 ft^2. All labs are equipped with networked computers for specimen tracking and data entry, the standard array of refrigerators, non-frost-free freezers, -20°C freezers, -80ºC freezers, deionized water and/or purifiers, balances, clinical and micro centrifuges, shakers, pipettes, etc. All are dedicated for sample receiving and processing, microbial culture, DNA/RNA extraction, and amplification and post-amplification molecular techniques. CAP/CLIA approved testing of bacterial vaginosis (vaginal Gram stain for Nugent score determination), *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, herpes simplex virus, and syphilis (RPR) occur in labs with devoted equipment. The research labs contain equipment and supplies committed to culture, research and developmental immunoserological and molecular testing for vaginal anaerobes, microaerophiles, capnophiles, *Candida spp*., *T. vaginalis*, *N. gonorrhoeae*, *C. trachomatis*, and *Mycoplasma genitalium*. In addition, these laboratories maintain several pieces of equipment of note: 1 inverted and 1 direct fluorescence microscope, 1 teaching microscope, 5 light microscopes, 3 CO_2 incubators, 4 standard incubators, 2 ELISA washers/readers, 1 anaerobe chamber, 10 Mitsubishi boxes, 1 gas chromatograph with autoinjector, 1 UV/Vis spectrophotometer, 1 vacufuge / lyophilizer, 2 thermocyclers, 5 horizontal electrophoresis units, 2 vertical electrophoresis units, 3 power units, 1 DGGE mutation detection electrophoretic system, 1 pulsed field gel electrophoresis (PFGE) system, 1 digital imager and appropriate software (Quantity 1 v.4.6.9), 1 GenProbe APTIMA, and 1 Roche COBASS. Should the need arise where appropriate equipment is not available, additional equipment and expertise can be accessed through one of the Core Facilities on the UAB campus.

Clinical Resources:

The Jefferson County Department of Health (JCDH) STD Clinic. The JCDH STD clinic, located adjacent to the UAB campus and the STD Research labs, serves as the main recruitment site for the UAB STD Research Group's clinical studies. It will also be the primary clinic site at UAB for the proposed RCT in Aim 1. Established in 1917, the JCDH is the largest local health department in Alabama. The JCDH STD clinic and the UAB ID division have a close working relationship and long history of collaboration. Medical coverage for the STD clinic is provided by four UAB STD faculty, including Dr. Muzny. The JCDH STD clinic is staffed by six UAB research nurse clinicians and five Health Department nurse clinicians. It is supported by a computerized medical record and a "stat" laboratory where Gram stains, wet mounts of vaginal fluid, qualitative serological tests for syphilis, urine pregnancy tests, and other microbiological studies including darkfield microscopy can be performed. Additional routine standard of care testing at the JCDH STD clinic includes APTIMA nucleic acid amplification testing (NAAT) for *T. vaginalis*, *C. trachomatis*, and *N. gonorrhoeae*, quantitative serological tests for syphilis, and HIV antibody testing. The Clinic also has 10 fully equipped examination rooms (each equipped with

networked computer terminals and all equipment and material required for patient care), two multi-purpose conference rooms, incubators, refrigerators, and -20º and -80º freezers available for media and specimen storage. A courier travels two to three times daily between the STD clinic and the UAB STD research labs, insuring timely and efficient transport of clinical and research specimens.

Louisiana State University (LSU)

Health Sciences Center

The LSU Health Sciences Center-New Orleans is uniquely positioned to support an intellectually stimulating environment that will ensure the success of this proposed project. Promoting a highly interactive and intellectually stimulating environment was a central goal of the design of the computational laboratory. Weekly meetings are also held in the laboratory to discuss sequencing on the MiSeq and informatics approaches between the computational scientists, biologists, and clinicians involved in the sequencing lab. LSUHSC is committed to further developing strong computational analysis and bioinformatics capabilities, which will help to ensure the success of the Bioinformatics laboratory.

Office Space:

Dr. Taylor has a private office located on the 6th floor of the Clinical Sciences Research Building (CSRB) at LSUHSC equipped with phone, computer, printer, and high-speed Internet access. LSUHSC has an administrative staff and information technology staff available to all researchers.

Computational Laboratory:

Dr. Taylor's computational laboratory occupies 470 square feet of space on the 6th floor of LSUHSC's Clinical Sciences Research Building (CSRB) divided into the main laboratory and an attached private office (described above). The open floor plan of the renovated computational laboratory has seven workstations situated around the perimeter of the lab equipped with high-performance multi-processor computers. A meeting table in the center of the room provides space for up to six participants meeting face-to-face and a ceiling-mounted drop down projection screen allows for presentation of slides and remote meeting participation. This laboratory setup provides an ideal venue for collaborative meetings where data analysis results can be viewed and discussed with collaborators. The computer lab is equipped with high-performance computing workstations connected via a local Gbps network router. A Synology DiskStation 12-Bay Network Attached Storage (NAS) houses 48 TB (12 x 4TB Enterprise Class HDDs) of secondary storage configured in a Synology hybrid RAID with 2-Disk redundancy providing 36.2 TB usable storage. The NAS is connected to the same Gbps router using 4 ethernet cables with link aggregation providing sufficient throughput to serve all of the workstations. Current workstations installed in the lab include:

- 6 x dual processor 2.7 GHz Twelve-Core Intel Xeons with 24 physical cores each (48 logical cores each), each equipped with 512 GB 1333Mhz DDR3 ECC RAM, a 512 GB SSD for the operating system and 18 TB of additional secondary storage (3 x 6TB 7200 rpm HDDs), and NVIDIA Quadro NVS 510 2 GB DDR3 Graphics Cards
- 1 x dual processor 2.0 GHz Eight-Core Intel Xeon with 16 physical cores (32 logical cores)**,** equipped with 128 GB 1600MHz DDR3 ECC RAM, 4 TB (2 x 2TB 7200 rpm HDDs) secondary storage, and an NVIDIA Quadro 4000 2 GB GDDR5 Graphics Card
- 1 x quad processor 2.4 GHz Eight-Core Intel Xeon with 32 physical cores (64 logical cores), equipped with 512 GB 1600Mhz DDR3 ECC RAM, 4.25 TB (4TB 7200 rpm HDD, 256 Gb SSD) secondary storage, and an NVIDIA Kepler 4000 3 GB GDDR5 Graphics Card

In total these 8 multi-processor, high performance workstations provide 192 physical computing cores (384 logical computing cores) available for distributed analysis of sequencing data. These computers run Ubuntu Linux 14.04.2 LTS (Trusty Tahr) and are equipped with all necessary analysis software and utilities. The machines are each protected by UPS for surge protection and battery backup. The Synology NAS is also protected by UPS and backed up to external storage.

Sequencing Laboratory: The sequencing laboratory occupies 1,210 square feet of space on the 7th floor of LSUHSC's Clinical Sciences Research Building (CSRB). Within the lab there are three rooms dedicated to DNA isolation, PCR preparation and sequencing. The lab is equipped with state-of-the-art instrumentation and provides a variety of genomic analyses including TaqMan real-time PCR, RNA/DNA extraction, purification and high-throughput Illumina MiSeq sequencing. A Clinical Specimen BSL-2 laboratory is available for processing human specimens. This facility is equipped with a laminar flow hood, refrigerated aerosol containment centrifuges, a cytospin, -80ºC freezer with liquid nitrogen back up, and a separate liquid nitrogen specimen

storage dewer. Animal or environmental samples undergo initial processing and nucleic acid isolation in a laminar flow hood. Specimens are aliquotted and back-up samples stored in separate containers.

University of Cape Town (UCT) School of Public Health and Family Medicine

Division of Health Economics and Health Economics Unit

The Health Economics Unit was established in 1990 as a research unit within the then Department of Community Health at the University of Cape Town. The unit aims to build equitable health systems in South Africa and beyond through teaching, research and policy engagement. The unit has an impressive research and policy engagement track record particularly in the areas of cost-effectiveness analysis and health financing. Teaching in Health Economics is housed within the Division of Health Economics, including a postgraduate diploma, Masters in Public Health and PhD specializations in Health Economics.

Office Space:
The unit/division occupies its own building adjacent to the School of Public Health and Family Medicine, in the Faculty of Health Sciences at UCT. Space includes 14 private offices, a room for postgraduate students and a boardroom with full videoconferencing facilities.

Computers, Telecommunications, IT:
All staff and students dedicated computers and printers. Departmental and University-wide network and internet access is available to all users, with centralized printing services and library and electronic journal access.

Administration and Grants Management:
Research management at the Health Economics Unit is supported by numerous operational and support staff with the capacity to address pre- and post-award financial management, including review, approval and processing of all transactions associated with the sub-contract of this award. This includes financial projections and reports, grants compliance, and control and monitoring of subject payments in a way that maximizes confidentiality as well as security of funds.

South African Medical Research Council (SA-MRC)

Maternal and Infant Health Care Strategies Research Unit:

The unit is an extramural unit of the SA-MRC in partnership with the University of Pretoria. The Unit has been in existence since 1997. The Unit specializes in identifying the core problems, developing effective solutions and determining successful ways of implementing interventions to reduce deaths of pregnant women and their infants at primary and secondary levels of care. This research has been closely linked with helping to achieve the Millennium Development Goals (MDGs) 4 and 5, and now is concentrating on the Sustainable Development Goals. The research mandate of the Unit has been to develop health strategies at primary and secondary care levels for mothers and infants by seeking sellable and sustainable solutions; by seeking we mean performing research, by saleable we mean solutions that are acceptable to women, health care workers and health administrators, and by sustainable solutions we mean health strategies that have been developed to solve the problems identified and how they can be sustained.

Office Space:
The Unit occupies a block an old nursing residence at Kalafong Provincial Tertiary Hospital. The agreement with the hospitals is that we will maintain the building and pay for its costs and the Hospital will not charge rent. There are at 20 workspaces along with all the other facilities. Furthermore the unit has space on the ground floor which can be used to see patients.

Computers, Telecommunications, IT:
The Unit has all the facilities necessary for modern communication, including high speed internet connect nodes. This infrastructure is maintained by the University of Pretoria.

Administration and Grants Management:

The University of Pretoria manages all the grants of the unit and we have an accountant who keeps our finances in order. The Unit has a fulltime programme manager who looks after the programmes on sites.

University of Cape Town (UCT) School of Medicine

Division of Medical Virology
UCT established the Institute of Infectious Disease and Molecular Medicine (IDM) in order to consolidate and expand major existing efforts to combat the most serious threats to health and overall prosperity in the region: infectious diseases including HIV/AIDS and TB and non-communicable diseases, and locally prevalent cancers and genetic disorders.

Laboratories & Equipment: The IDM has over 8000 square metres of laboratory space.In the areas that fall under the management of Prof Williamson that are available for this project: there is a 91m^2 dedicated Biosafety level-2 (BSL-2) molecular biology laboratory, a separate and dedicated PCR clean room, a separate and dedicated nucleic acid extraction room and a dedicated laboratory (BSL-2) to work with clinical material. The laboratories are located on the third floor of the Wernher Beit South Building at UCT. The molecular biology laboratory has standard equipment including micro-centrifuges, monitored fridges and freezers, BSL-2 safety cabinets, thermal cyclers, gel electrophoresis equipment, Dark Reader Illuminator. All freezers are connected to a 24-hour monitoring system. Access is available to Roche MagNA Pure Compact System, multiple conventional and gradient thermal cyclers, a FLUOstar OPTIMA (BMG Labtech) fluorescence microplate reader, NanoDrop and a Quantstudio 7 real-time PCR system and Roche LightCycler. A walk-in cold room (4°C) and freezer room (-20°C) are available for storage. Glassware washing and autoclave facilities are located on the same floor.

Office: Private Departmental offices for Dr Meiring and shared offices for senior scientists, postdocs, technologists and students are on the third floor of IDM, UCT. The building is secure with access control via individual identification cards. Every office is networked with one telephone connection and one or more desktop computer facilities.

Computers and Software: All staff, students and post-doctoral fellows have dedicated computers and printers. Departmental and University-wide network and internet access is available to all users, with centralized printing services and library and electronic journal access. High Performance Computing (HPC) laboratory: The University of Cape Town's Information and Communication Technology Services (ICTS) High Performance Computing (HPC) laboratory provides free computing resources and support to scientific computing users at UCT. The facilities and setup include 564 cores, large memory machines, Tesla M2090 GPUs, 25TB storage, Infiniband interconnect and OpenMPI Architecture. The ICTS HPC has also integrated their cluster resources into the South African National Computing Grid. Support is available for the installation and configuration of scientific applications (custom written, open source or commercial) on the HPC nodes, for modification of packages to grid format facilitating access to more computing resources and providing assistance for parallel coding requirements. H3 African bioinformatics network (H3ABioNet): The H3ABioNet was awarded to Prof Mulder of the Computational Biology Division and IDM. Our ties to this African bioinformatics network for H3Africa within the IDM will provide additional computing resources and access to cloud computing should this be required.

Administration and Grants Management: Research management at IDM is supported by numerous operational and support staff with the capacity to address pre- and post-award financial management, including review, approval and processing of all transactions associated with the sub-contract of this award. This includes financial projections and reports, grants compliance, and control and monitoring of subject payments in a way that maximizes confidentiality as well as security of funds.

Anova Health Institute / University of Pretoria Department of Medical Microbiology

Anova Health Institute is a South African-based non-governmental organization that receives its main funding from PEPFAR through USAID. The organization works as district support partner in various regions of South Africa and has a large portfolio of HIV, TB and STI implementation programs in the public healthcare sector. Anova's research portfolio is built around the same program areas. For microbiological research, Anova has a longstanding collaboration with the Department of Medical Microbiology at the University of Pretoria as

evidenced by a large number of successful joint research projects. Prof Peters jointly works with Anova and the University of Pretoria Department of Medical Microbiology to ensure a strong collaborative relationship as well as access to and supervision of microbiological laboratory work.

Office Space:
Prof Peters occupies an office at the Anova Health Institute at 12 Sherborne Road, Parktown Johannesburg. In addition, he has a designated office space at the University of Pretoria, Department of Medical Microbiology in the Pathology Building (Room 3.11). There is ample space for storage of research documentation, consumables and resources.

Computers, Telecommunications, IT:
Prof Peters and laboratory staff all have computers, printers, telephone, email communication, and copying capabilities; both at Anova and at UP.

Administration:
Ms Linda McConnell is the Chief Executive Officer at Anova Health Institute and responsible for managing all donor organizations and all funds received by the organization. There is a specific compliance division at Anova who ensures that all criteria for good financial management are met.

Laboratory resources
The infrastructure to support this research project exists at the Department of Medical Microbiology, University of Pretoria/NHLS. This includes: SANAS accredited laboratories, specialized equipment for molecular analysis, skilled and trained technologists, clinicians and researchers, Internet access, E-mail and library facilities. The required allocated diagnostic and research laboratories as well as the necessary equipment which include: Biosafety cabinets, centrifuges, heating blocks, thermocyclers, Roche Version 2 LightCycler (Virtual Laboratory) and a Roche 480 LightCycler for Real-Time PCR platforms, Rotaphor PFGE system and the Bionumerics (GelCompar part) programme required for the genotypying analysis. Senior research team members will insure regular meetings and assessment of results to support and train junior researchers.

EQUIPMENT

Rooms to be used as office space are limited at the clinics. Therefore, in year 1, FPD will purchase a truck container, for use at one site without sufficient space for study purposes. This truck container, commonly in use in South Africa, is 12m (39.3ft), with windows, door, electrics and air-conditioning.

Photos of a sample unit are below.

Additionally, following items are available to Dr. Muzny within the UAB STD Research Laboratories at the University of Alabama at Birmingham. These laboratories are located in the Tinsley Harrison Tower (2 labs, 1,500+ sq. ft.), Zeigler Research Building (11 labs, 2,500+ sq. ft.), and Lyons Harrison Building (7 labs, 2,000+ sq. ft.). Additional freezer storage space (350 sq. ft.) is located in the McCallum building which is adjacent to the Tinsley Harrison Tower.

- Biosafety hoods (3)
- CO_2 incubators for cell culture and bacterial culture (4)
- Water baths (4)
- -20° freezers (6)
- -80° freezers (8)
- Zeiss fluorescence microscopes (1 inverted, 1 direct)
- Light microscopes (6)
- Stereoscopic dissecting microscope
- High speed centrifuge, microfuges (4)
- Table-top centrifuge suitable for clinical samples
- Thermal cyclers for PCR (3)
- Cytobrite Slide incubation system (Scigene)
- C24 Incubator shaker (New Brunswick Scientific)
- Equipment for genetic analysis including PFGE and DGGE
- Microplate washers and readers for ELISA measurements (2)
- CFX96 real time PCR system (Biorad) for running quantitative PCR assays
- Nanodrop
- E-Gel Power Snap system
- Syphilis serology equipment
- Gonococcal culture equipment
- Hologic Panther for chlamydia/gonorrhea/trichomonas RNA detection
- BD Viper for chlamydia/gonorrhea/trichomonas nucleic acid amplification assays (NAATs)
- Cepheid GeneXpert for chlamydia/gonorrhea/trichomonas NAATs
- Roche Cobas4800 and 6800 for chlamydia/gonorrhea/trichomonas/*Mycoplasma genitalium* NAATs; The the Cobas4800 system includes a Light Cycler Z480 that has open software that can be used to perform laboratory developed assays
- Computers for data entry (4)
- Usual array of autoclaves, biosafety cabinets, ice machines, balances, clinical centrifuges, shakers, pipettes, etc.

The following equipment is available to Dr. Taylor at the LSU Health Sciences Center (LSUHSC) for the purposes of vaginal microbiome research:

<u>Sequencing Laboratory (LSUHSC-NO 7th Floor CSRB):</u>

- Bio-Rad iCycler IQ Multicolor Real-Time PCR Detection System (Bio-Rad)
- Illumina Mi-Seq Benchtop Sequencer
- Agilent 2100 Bioanalyzer
- Thermal Cyclers (ABI GeneAmp 9700; BioRad)
- Spectrophotometer (NanoDrop)
- Veritas Microplate Luminometer (Turner Biosystems)
- FLx800 Microplate Fluorescence Reader (BioTek Instruments)
- Particle counter (Beckman)
- TissueLyser (Qiagen)
- Vacuum pump (Roche)
- Microcentrifuge (1000-16000 RCF) (Eppendorf)
- BioRad Bio-Plex system
- Clinical Specimen BSL-2 laminar flow hoods (LABCONCO)
- PCR hoods

- Refrigerated aerosol containment centrifuges (Eppendorf)
- Mini-plate spinner (Labnet)
- Shandon Cytospin4 (Thermo)
- Gel imager (Bio Rad)
- Upright microscope (Motic)
- Autoclave
- Ice makers
- Centrifuge with swing bucket rotor (Eppendorf)
- Freezers (-80ºC, -20ºC) and Refrigerators (4ºC)
- Ultra pure water maker (Millipore)
- ABI Prism 7900HT Sequence Detection Systems
- Affymetrix GeneChip platform and bioinformatics system, including a LIMS server
- BioRad CFX 96 real time PCR machine
- BioRad Opticon

Standard, Positive Pressure, Germ-Free, Flexible Film Isolator (Class Biologically Clean Ltd)

Computational Laboratory (LSUHSC-NO 6th Floor CSRB):

- (6) Dual-Processor 2.7 GHz Twelve-Core Intel Xeons (24 physical cores each, 48 logical cores each) with 512 GB 1333 MHz DDR3 ECC RAM each, 512 GB SSD each, 18 TB HDD each, NVIDIA Quadro NVS 510 2 GB DDR3 Graphics Card each, and 24x DVD+/-RW drive each
- Dual-Processor 2.0 GHz Eight-Core Intel Xeon (16 physical cores, 32 logical cores) with 128 GB 1600 MHz DDR3 ECC RAM, 4 TB (2 x 2TB 7200 rpm HDDs) secondary storage, NVIDIA Quadro 4000 2 GB GDDR5 Graphics Card, 24x DVD+/-RW drive
- Quad-Processor 2.4 GHz Eight-Core Intel Xeon (32 physical cores, 64 logical cores) with 512 GB 1600 MHz DDR3 ECC RAM, 4.25 TB (4TB 7200 rpm HDD, 256 GB SSD) secondary storage, NVIDIA Kepler 4000 3 GB GDDR5 Graphics Card, 24x DVD+/-RW drive
- Synology Diskstation 12-Bay Network Attached Storage which can scale up to 100 TB of secondary storage
- APC Back-UPS 750
- (7) APC Back-UPS PRO 1500
- APC SMC1500 Smart-UPS

FOREIGN JUSTIFICATION

Our study team has outstanding, well-documented experience in the conduct and in-depth analysis of clinical cohort and laboratory studies for many years. Specifically, PIs Klausner and Medina-Marino have collaborated successfully on grants, publications, NIH-Fogarty training and infectious disease/ reproductive health projects since first meeting and working together at CDC-PEPFAR South Africa in 2010. Their current successful R21 (2015-2017) from NICHD directly informs this new proposal. That R21 is a pilot study that integrates molecular diagnostic testing for CT, NG and TV into antenatal care (ANC) services for HIV-infected pregnant women in South Africa. In that study, we found that diagnostic screening and targeted treatment (TT) during ANC was highly acceptable and feasible; 97.8% of all eligible women agreed to be tested, and >93% with an STI received same-day treatment. Importantly, we found a 41% STI prevalence in this patient population, of which 65% of infections were asymptomatic, demonstrating the importance of testing STI interventions among this patient population.

Overall, HIV and STIs among pregnant women in South Africa are a major problem. In 2013, the South African government estimated that 29.7% of women seeking antenatal care were HIV-infected, a prevalence that has remained relatively stable since 2007. That high HIV prevalence is compounded by high rates of STIs in women of reproductive age. Given that most STIs in women are asymptomatic and that the South African government currently only recommends symptomatic screening and syndromic management in line with WHOs global guidelines, the majority of STIs in HIV+ South African pregnant women go undiagnosed and untreated.

Our study will enhance knowledge of STIs during pregnancy, especially among high HIV prevalence populations, and the effectiveness of routinizing same-day PCR screening and treatment for these STIs in reducing adverse pregnancy and birth outcomes. Furthermore, until now there have been no studies in low and middle-income countries that have evaluated the costs and benefits of CT/NG/TV screening and treatment during pregnancy as it relates to pregnancy, neonatal and infant outcomes. Our cost/cost-effectiveness study has the potential to influence health policy in South Africa and globally, especially as it compares to syndromic management of STIs during pregnancy. If successful, this study would also provide reproducible cost-effectiveness analysis models for countries to better plan for and implement routine CT/NG screening and treatment in pregnancy.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Jeffrey Middle Name Last Name*: Klausner Suffix: MD

Position/Title*:	Professor
Organization Name*:	UCLA David Geffen School of Medicine
Department:	Medicine
Division:	Infectious Diseases
Street1*:	9911 West Pico Blvd
Street2:	Suite 955
City*:	Los Angeles
County:	Los Angeles County
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90035-2738

Phone Number*: 310-557-3044 Fax Number: 310-557-3679 E-Mail*: JDKlausner@mednet.ucla.edu

Credential, e.g., agency login: jklausner

Project Role*: PD/PI Other Project Role Category:

Degree Type: Degree Year:

	File Name
Attach Biographical Sketch*:	Biosketch_Klausner1054114384.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Andrew Middle Name Last Name*: Medina-Marino Suffix: PhD

Position/Title*:	Head of Research Unit
Organization Name*:	Foundation for Professional Development
Department:	
Division:	
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City*:	The Willows
County:	
State*:	
Province:	
Country*:	ZAF: SOUTH AFRICA
Zip / Postal Code*:	

Phone Number*: +27 (0) 12 816 9000 Fax Number: E-Mail*: andrewm@foundation.co.za

Credential, e.g., agency login: AMEDINA-MARINO

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2009

	File Name
Attach Biographical Sketch*:	Biosketch_Medina_Marino1054050490.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Christopher Middle Name Last Name*: Taylor Suffix: PhD

Position/Title*:	Associate Professor
Organization Name*:	Louisiana State University Health Sciences Center - NO
Department:	School of Medicine
Division:	Microbiology, Immunology
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City*:	New Orleans
County:	Orleans
State*:	LA: Louisiana
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	70112-2256

Phone Number*: 504-568-4065 Fax Number: 504-568-2918 E-Mail*: ctay15@lsuhsc.edu

Credential, e.g., agency login: CHRISTAYLOR

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2008

	File Name
Attach Biographical Sketch*:	Biosketch_Taylor1054050492.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Susan Middle Name Last Name*: Cleary Suffix: PhD

Position/Title*:	Associate Professor
Organization Name*:	University of Cape Town
Department:	Health Economics
Division:	
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County:	
State*:	
Province:	
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Zip / Postal Code*:	

Phone Number*: +27 21 406 6755 Fax Number: E-Mail*: susan.cleary@uct.ac.za

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2007

	File Name
Attach Biographical Sketch*:	Biosketch_Cleary1054050494.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Robert Middle Name Last Name*: Pattinson Suffix: MD

Position/Title*:	Director
Organization Name*:	University of Cape Town
Department:	Obstetrics and Gynecology
Division:	
Street1*:	Atteridgeville, 0008
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County:	
State*:	
Province:	
Country*:	ZAF: SOUTH AFRICA
Zip / Postal Code*:	

Phone Number*: +27 12 318 6400 Fax Number: E-Mail*: robert.pattinson@up.ac.za

Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1992

	File Name
Attach Biographical Sketch*:	Biosketch_Pattinson1054050496.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Koleka Middle Name Last Name*: Mlisana Suffix: PhD

Position/Title*:	Executive Manager
Organization Name*:	University of KwaZulu Natal
Department:	Medicinal Microbiology
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Credential, e.g., agency login:

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2014

	File Name
Attach Biographical Sketch*:	Biosketch_Koleka1054050497.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Christina Middle Name Last Name*: Muzny Suffix: MD

Position/Title*:	Associate Professor
Organization Name*:	University of Alabama
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Province:	
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Zip / Postal Code*:	35233-0007		
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Credential, e.g., agency login: CMUZNY			
Project Role*: Co-Investigator		Other Project Role Category:	
Degree Type: MD		Degree Year: 2003	
		File Name	
Attach Biographical Sketch*:		Biosketch_Muzny1054050498.pdf	
Attach Current & Pending Support:			

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: David Middle Name T Last Name*: Redden Suffix: PhD

Position/Title*:	Professor
Organization Name*:	University of Alabama
Department:	Biostatistics
Division:	
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Street2:	1720 2nd Ave South
City*:	Birmingham
County:	Jefferson
State*:	AL: Alabama
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	35233-0007

Phone Number*: 205-975-9165	Fax Number: 205-975-2540	E-Mail*: dredden@uab.edu
Credential, e.g., agency login:		
Project Role*: Co-Investigator		Other Project Role Category:
Degree Type: PhD		Degree Year: 1995
		File Name
Attach Biographical Sketch*:		Biosketch_Redden1054050553.pdf
Attach Current & Pending Support:		

BIOGRAPHICAL SKETCH

NAME: Jeffrey D. Klausner, MD, MPH

eRA COMMONS USER NAME (credential, e.g., agency login): jklausner

POSITION TITLE: Professor of Medicine and Public Health

EDUCATION/TRAINING*:*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University, Ithaca, New York	A.B.	06/1986	Chemistry and Art
Cornell University Medical School, New York, NY	M.D.	06/1991	Medicine
Harvard School of Public Health, Boston, MA	M.P.H.	06/1995	International Health
Centers for Disease Control and Prevention, GA	EIS	06/1997	Epidemiology
University of Washington, Seattle, WA	Fellow	06/1998	Infectious Diseases

A. Personal Statement

Jeffrey D. Klausner, MD, MPH, is a board-certified internist, infectious disease specialist, and internationally recognized infectious disease researcher and expert in the prevention, control and epidemiology of HIV infection and other sexually transmitted diseases. Dr. Klausner is the Senior Editor of the McGraw-Hill Lange textbook *Current Diagnosis and Management of Sexually Transmitted Diseases*. Dr. Klausner is a member of the WHO STI Treatment Guidelines work group and plays a leadership advisory role in the WHO congenital syphilis elimination effort. He is a frequently invited speaker at national and international meetings on HIV and STDs. From 2009-2011 Dr. Klausner was the Branch Chief for the US CDC PEPFAR HIV and TB program in Pretoria, South Africa, the location of the proposed study. Upon his return to the US, he accepted a senior faculty position at UCLA in infectious disease research and global health with a particular focus on global women's health and infections in pregnancy. Dr. Klausner has served as Principal Investigator for numerous CDC, NIH and industry sponsored clinical trials and HIV/STD prevention studies and is Chair of the NIH/DMID STI Clinical Trials Group. This current proposal builds directly on his interest in furthering the understanding of the host and responses to STIs among HIV-infected pregnant women and his recent studies of infections in pregnant women in Botswana, Congo, South Africa, Vietnam, India, Haiti and Peru.

Dr. Klausner has known and collaborated with Dr. Medina-Marino since 2010, mentoring trainees, implementing USAID, CDC and NIH-funded research and co-authoring publications. As the Principal Investigator and STI clinical expert on this project, he will co-lead with Dr. Medina-Marino the oversight, design, implementation, and analysis of this study.

B. Positions and Honors

1991-1994	Intern and Resident, Medicine, NYU-Bellevue Hospital Center, NY
1995-1997	Officer, Epidemic Intelligence Service, Centers for Disease Control, Atlanta, GA
1997-1998	Senior Clinical Fellow, Infectious Diseases, University of Washington, Seattle, WA
1998-2004	Assistant Clinical Professor of Medicine, University of California, San Francisco
1998-2005	Medical Director, San Francisco City Clinic, San Francisco municipal STD Clinic
1998-2009	Director, San Francisco, Department of Public Health, STD Services
2004-2011	Associate Clinical Professor of Medicine, University of California, San Francisco
2009-2012	Member, WHO workgroup HIV and STD prevention for MSM/Transgender persons
2009-2011	Chief, HIV and TB Branch, Centers for Disease Control, South Africa
2012-Present	Professor of Medicine, University of California, Los Angeles
2013-Present	Professor of Public Health, University of California, Los Angeles
2013-Present	Member, WHO workgroup STI Treatment Guidelines

2002	San Francisco Suicide Prevention Community Award
2002	American STD Association, Young Investigator Award
2006	UCSF Association of Clinical Faculty Special Recognition Award

2009 Beyond AIDS Nettie Award
2010 Bay Area's Top Doctors and Dentists Award, Internal Medicine
2010 *Clinical Infectious Diseases* Award for Outstanding Review
2016 CDC Jack N. Spencer Career Achievement Award

C. Contributions to Science

1. Curable Infections in pregnant women: Since returning to the U.S. in 2012, I have launched a program to study the acceptability, feasibility, prevalence and outcomes of screening for curable STIs in pregnant women. I have completed studies in Peru, Haiti, India, Vietnam, Congo, Botswana and South Africa demonstrating the high acceptability of STI testing with self-collected vaginal swabs, the excellent performance of point-of-care PCR assays and the high frequency of treatment, partner treatment and clearance of infection. As a member of the WHO STI Guidelines Committee we are reviewing those and other data in anticipation of recommendations for universal STI screening in pregnancy.

a. Cabeza J, García PJ, Segura E, García P, Escudero F, La Rosa S, León S, **Klausner JD**. Feasibility of Chlamydia trachomatis screening and treatment in pregnant women in Lima, Peru: a prospective study in two large urban hospitals. Sex Transm Infect. 2015 Feb;91(1):7-10. doi: 10.1136/sextrans-2014-051531. PMID: 25107711; PMCID: PMC4417475.
b. Wynn A, Ramogola-Masire D, Gaolebale P, Moshashane N, Agatha Offorjebe O, Arena K, **Klausner JD**, Morroni C. Acceptability and Feasibility of Sexually Transmitted Infection Testing and Treatment among Pregnant Women in Gaborone, Botswana, 2015. Biomed Res Int. 2016;2016:1251238. doi: 10.1155/2016/1251238. PMID: 27119076; PMCID: PMC4826911.
c. Bristow CC, Mathelier P, Ocheretina O, Benoit D, Pape JW, Wynn A, **Klausner JD**. Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis screening and treatment of pregnant women in Port-au-Prince, Haiti. Int J STD AIDS. 2017 Jan 1:956462416689755. doi: 10.1177/0956462416689755. PMID: 28134005.
d. Mudau M, Peters RP, De Vos L, Olivier DH, J Davey D, Mkwanazi ES, McIntyre JA, **Klausner JD**, Medina-Marino A. High prevalence of asymptomatic sexually transmitted infections among human immunodeficiency virus-infected pregnant women in a low-income South African community. Int J STD AIDS. 2017 Jan 1. doi: 10.1177/0956462417724908. PMID: 28799824.

2. Point-of-care and near care diagnostic testing for STIs: With over 500 million annual curable sexually transmitted infections (STIs) globally, STIs remain a common and preventable means of adverse pregnancy and birth outcomes. Prematurity is the leading cause of under age 5 years mortality and undiagnosed and untreated STIs are one of the most significant causes of prematurity. New diagnostics that are inexpensive, easy-to-use and accurate are urgently needed in low and middle income countries. Since the mid-2000s, I have been researching, developing and evaluation point-of-care diagnostics for HIV, syphilis, chlamydial and gonococcal infections (*CID*, 2008, *Trop Med Int Health* 2009, *PloS One* 2013, *Open Forum ID* 2014). Currently I have STI screening projects in Democratic Republic of Congo, Botswana, South Africa, Haiti and India building upon and extending earlier findings of high-rates of curable STIs in pregnancy associated with adverse pregnancy and birth outcomes including increased rates of mother-to-child transmission of HIV infection. Using those data, I aim to conduct clinical trials demonstrating the impact and cost-benefit of STI screening and treatment in pregnancy in low and middle income country settings.

a. Philip SS, Ahrens K, Shayevich C, de la Roca R, Williams M, Wilson D, Bernstein K, **Klausner JD**. Evaluation of a new point-of-care serologic assay for herpes simplex virus type 2 infection. Clin Infect Dis. 2008 Nov 15;47(10):e79-82. doi: 10.1086/592696. PMID: 18840082.
b. Madhivanan P, Krupp K, Hardin J, Karat C, **Klausner JD**, Reingold AL. Simple and inexpensive point-of-care tests improve diagnosis of vaginal infections in resource constrained settings. Trop Med Int Health. 2009 Jun;14(6):703-8. doi: 10.1111/j.1365-3156.2009.02274.x. Epub 2009 Apr 20. PMID: 19392745; PMCID: PMC3625926.
c. Pilcher CD, Louie B, Facente S, Keating S, Hackett J Jr, Vallari A, Hall C, Dowling T, Busch MP, **Klausner JD**, Hecht FM, Liska S, Pandori MW. Performance of rapid point-of-care and laboratory tests for acute and established HIV infection in San Francisco. PLoS One. 2013 Dec 12;8(12):e80629. doi: 10.1371/journal.pone.0080629. eCollection 2013. PMID: 24349007; PMCID: PMC3861178.

d. Bristow CC, Leon SR, Ramos LB, Vargas SK, Flores JA, Konda KA, Caceres CF, **Klausner JD**. Laboratory Evaluation of a Dual Rapid Immunodiagnostic Test for HIV and Syphilis Infection. Journal of clinical microbiology. 2014. Epub 2014/11/08. doi: 10.1128/jcm.02763-14. PMID: 25378568.

3. Pathophysiology and clinical aspects of syphilis: There are 6 million new cases of syphilis annually and a current exponentially growing epidemic of syphilis among men who have sex with men. Since first describing the elimination and re-introduction of syphilis in Seattle-King County in 1999 (*Am J Pub Health*, 1999), I have been one of the leading public health researchers describing clinical manifestations and pathogenesis of the disease and creating and evaluating new interventions to control syphilis and (*AIDS* 2004, *BMC ID* 2013; *STD* 2015). Based on my research and those replicated by others, the US DHHS recommendations for syphilis screening in HIV-infected patients include testing every 3-6 months. Furthermore, based on my prior clinical studies, the CDC STD Guidelines include recommendations for the use of both treponemal and non-treponemal testing in patient presenting symptomatically, in particular with primary stage manifestations. Currently I provide guidance in the frequency and type of STD screening in patients on Pre Exposure Prophylaxis or PrEP for HIV infection. My earlier work describing the frequency and clinical outcomes of patients with azithromycin-resistant syphilis infection resulted in the removal of azithromycin as recommended alternative therapy in patients with syphilis. My published work on the effectiveness of doxycycline treatment provided evidence to maintain doxycycline as a recommended alternative treatment.

a. Williams LA, **Klausner JD**, Whittington WL, Handsfield HH, Celum C, Holmes KK. Elimination and reintroduction of primary and secondary syphilis. Am J Public Health. 1999 Jul;89(7):1093-7. PMID: 10394323; PMCID: PMC1508824.
b. Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD, **Klausner JD**. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS. 2004 Oct 21; 18(15): 2075-9. PMID: 15577629.
c. Jinno S, Anker B, Kaur P, Bristow CC, **Klausner JD**. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. BMC Infect Dis. 2013 Dec 26;13:605. doi: 10.1186/1471-2334-13-605. PMID: 24369955; PMCID: PMC3877955
d. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, **Klausner JD**. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. Sex Transm Dis. 2015 Feb;42(2):98-103. doi: 10.1097/OLQ.0000000000000216. PMID: 25585069; PMCID: PMC4295649.

4. Biomedical HIV Prevention: HIV infection continues to be hyper-epidemic in high-risk populations globally with annual incidence rates of 5-10%. Biomedical prevention and combinations thereof—testing, treatment and male circumcision—offer the best opportunity for reducing population-level incidence. From conducting early acceptability studies in various populations to describing the epidemiology of male circumcision in California (*PLoS One* 2007, *STD*, 2011), I have been a leading researcher and advocate informing the evidence base for newborn and adult male circumcision (*Science*, 2008).

a. Kojima N, Bristow C, Pollock N, Crouse P, Theodore H, Bonhomme J, Gaston C, Devieu J, J Pape, **Klausner, JD**. Rapid Training and Implementation of the Pollock Technique, a Safe, Effective Newborn Circumcision Procedure, in a Low-Resource Setting. Global Pediatric Health. Published June 11, 2015, January-December 2015 vol. 2 2333794X15589114. PMID: 27335959, PMCID: PMC4784613.
b. Madhivanan P, Krupp K, Kulkarni V, Kulkarni S, **Klausner JD**. Acceptability of male circumcision for HIV prevention among high-risk men in Pune, India. Sex Transm Dis. 2011 Jun;38(6):571. doi: 10.1097/OLQ.0b013e318219c930. PMID: 21836398.
c. Potts M, Halperin DT, Kirby D, Swidler A, Marseille E, **Klausner JD**, Hearst N, Wamai RG, Kahn JG, Walsh J. Public health. Reassessing HIV prevention. Science. 2008 May 9;320(5877):749-50. doi: 10.1126/science.1153843. PMID: 18467575; PMCID: PMC3501984.
d. **Klausner JD**. Newborn circumcision: ensuring universal access. Sex Transm Dis. 2013 Jul;40(7):526-7. doi: 10.1097/01.OLQ.0000431046.28649.23. PMID: 23965764.

5. Internet, social media and HIV/STD prevention: Networks of interconnected persons are critical to the introduction and spread of infectious diseases, in particular those transmitted through sexual activity. In 2000 I described the first outbreak of syphilis related to men meeting partners in an Internet chat room (JAMA, 2000) and went on to develop and evaluate Internet-based interventions for disease control (AIDS Care, 2004; STD

2005; PloS Med 2008). In 2004, I started "AskDrK.org," at the time one of the most popular sites for up-to-date and clear sexual health information for adolescents and sexual minorities. The Internet and social media have since become the *sine qua non* opportunity for health education and interventions to reach high risk groups regarding sexual and reproductive health.

a. **Klausner JD**, Wolf W, Fischer-Ponce L, Zolt I, Katz MH. Tracing a syphilis outbreak through cyberspace. JAMA. 2000 Jul 26;284(4):447-9. PMID: 10904507.
b. **Klausner JD**, Levine DK, Kent CK. Internet-based site-specific interventions for syphilis prevention among gay and bisexual men. AIDS Care. 2004 Nov;16(8):964-70. PMID: 15511728.
c. McFarlane M, Kachur R, **Klausner JD**, Roland E, Cohen M. Internet-based health promotion and disease control in the 8 cities: successes, barriers, and future plans. Sex Transm Dis. 2005 Oct;32(10 Suppl):S60-4. Review. PMID: 16205295.
d. Levine D, Woodruff AJ, Mocello AR, Lebrija J, **Klausner JD**. inSPOT: the first online STD partner notification system using electronic postcards. PLoS Med. 2008 Oct 21;5(10):e213. doi: 10.1371/journal.pmed.0050213. PMID: 18942887; PMCID: PMC2570420.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/jeffrey.klausner.1/bibliography/47475064/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIH-NIAID-R01AI139265 PI: Klausner and Caceres 09/01/2018-08/31/2022
Title: Syphilis immunology and biology to improve clinical management and vaccine design
Role: Principal Investigator
Goal: Describe new immune correlates of seroprotection against syphilis

NIH-NIDA-CTN-0083 PI: Klausner 06/01/2018-05/31/2020
Title: Using Social Media to Deliver HIV Self-Testing Kits and Link to Online PrEP Services
Role: Principal Investigator of NIDA Clinical Trial Network sub-study
Goal: Determine effectiveness of various Internet platforms for promoting HIV self-testing and PrEP uptake

NIH-NIMH-R01MH114891 PI: Wray 12/01/2017-10/31/2022
Title: Mobile health platform for providing real-time follow-up after home-based HIV self-testing
Role: Co-Investigator for Los Angeles site
Goal: Evaluate impact of electronic home-based HIV self-test

NIH-Fogarty-D43TW009343 PI: Cohen 07/01/2017-06/30/2022
Title: The University of California Global Health Institute (UCGHI)
Role: Principal Investigator for UCLA
Goal: The UCGHI brings together UCSF, UCSD, UCLA and UC Davis, along with a network of 20 collaborating international institutions to form the UCGHI GloCal Health Fellowship (GloCal) training program.

NIH-NICHD-U19HD08988 PI: Rotheram-Borus 9/30/2016-9/29/2021
Title: Adolescent Trials Network: A Comprehensive Community-based Strategy to Optimize the HIV Prevention and Treatment Continuum for Youth At HIV Risk, Acutely Infected and with Established HIV Infection
Role: Co-investigator
Goal: Follow youth aged 12-24 at the highest risk of acquiring HIV in Los Angeles and New Orleans, to optimize the HIV prevention continuum

NIH-NIAID-SBSS-DMID-NIHAI201112 PI: Klausner 07/01/2013-06/30/2020
Title: Sexually Transmitted Infection Clinical Trials Group, 2013-2020
Role: Principal Investigator responsible for study network implementation
Goal: Implement clinical prevention and treatment trials in STIs

Social Scientific Systems, Inc.HHSN272201300014I PI: Klausner 07/14/2017-05/13/2019

Title: Clinical Study of a Single-Use, POC Molecular Diagnostic Device for the Detection of NG, TV and CT Utilizing Vaginally Collected Swabs
Role: Co-Investigator
Goal: Evaluate rapid point-of-care STI

Recently Completed Research Support

NIH-NIAID-UM1AI104681 PIs: Chambers and Fowler 11/01/2014-10/31/2018
Title: Antibiotic Resistance Leadership Group
Role: Co-investigator/ Protocol Chair of Extra-genital CT/NG study
Goal: Evaluate various approaches to addressing antibiotic resistant infections

NIH/NIMH-R34MH106359 PI: McCoy 7/1/2015 – 6/30/2018
Title: Advancing HIV Prevention and Linkage to Care Among MSM with Gamification
Role: Co-Investigator
Goal: We developed and piloted an intervention that used the novel approach of gamification, the use of game elements in non-game contexts, to encourage young high-risk MSM to be regularly screened for HIV.

NIH-NIAID-1R21AI117256-01A1 PI: Klausner 04/2016-03/2018
Title: Reducing Excess Broad-Spectrum Antibiotic Use in Gonorrhea
Role: Principal Investigator responsible for overall study implementation
Goal: Evaluate a novel approach to controlling the spread of drug-resistant *N. gonorrhoeae*

Social Scientific Systems, Inc.-CRB-SSS-S-15-004631 PI: Klausner 08/2015-03/2018
Title: Sparing the Last Line of Antibiotics through Ciprofloxacin Susceptibility-Based
Role: Principal Investigator
Goals: Evaluate molecular gonorrhea resistance assay

NIH-NICHD-R21HD084274-01 PI: Klausner 9/2015-8/2017
Title: Pilot Study of STI Screening and Treatment for PMTCT, South Africa
Role: Principal Investigator responsible for overall study implementation
Goal: Evaluate the impact of STI point-of-care screening and treatment on birth and newborn outcomes

NIH-NIAID-R21AI120838 PI: Shin 08/2015-7/2017
Title: Utility of Deep Sequencing for Detecting Heteroresistant MTB Infections among HIV infected Persons
Role: Co-investigator assisting with study design and epidemiologic analysis
Goal: Determine the frequency and impact of multiple MTB infections

NIH/NIAID. 1R01AI099727 PI: Caceres 07/2012-06/2017
Title: Syphilis: Translating technology to understand a neglected epidemic
Role: Co-director of project responsible for overall implementation with specific emphasis on biologic measures.
Goal: Increase research capacity in Lima, Peru, through studying syphilis in high-risk men

CDC-200-2013-N15562 PI: Montoya 09/2013-06/2017
Title: A Waiting Room-Delivered Video to Enhance ART Care Continuum for HIV-Positive Minority Persons
Role: Co-investigator for video development and evaluation
Goal: Develop and evaluate a brief video to increase clinic retention in high-risk HIV-infected patients

NIH-NIAID-5R21AI109005-02 PI: Klausner 08/2014-03/2017
Title: Controlling Drug Resistant Gonorrhea with Real-Time PCR Susceptibility Testing
Role: Principal Investigator responsible for overall study implementation
Goal: Investigate use of real-time PCR to determine antimicrobial susceptibility of gonorrhea infections

Gilead Sciences PI: Klausner 10/2015-09/2016
Title: Enhancing the continuum of care for persons with hepatitis C in a large healthy system
Role: Principal investigator responsible for project implementation and overall evaluation
Goal: Through health system strengthening increase the detection and cure of persons with hepatitis C

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Andrew G.A. Medina-Marino, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): AMEDINA-MARINO

POSITION TITLE: Head, Research Unit, Foundation for Professional Development (FPD)

EDUCATION/TRAINING*:*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Swarthmore College	B.A.	06/2000	Biology/Race Relations
California Institute of Technology	M.S.	06/2003	Molecular Biology
Johns Hopkins University, School of Public Health	Certificate	06/2006	Infectious Diseases
California Institute of Technology	PhD	06/2009	Molecular Biology
U.S. Centers for Disease Control and Prevention	EIS	06/2011	Epidemiology

A. Personal Statement

I am a molecular biologist and epidemiologist. As Head of FPD's Research Unit, I am the PI or co-investigator for a number of large NIH and USIAD funded research studies (see Ongoing Research Support section below). As Senior Technical Advisor for Disease Surveillance and Laboratory Systems, I work directly with a number of South Africa's 52 health districts to support systems strengthening activities focused on 1) assessing and enhancing pre- and post-analytical laboratory service at the clinic-lab interface, 2) capacity development to detect and respond to disease outbreaks, 3) supporting the use of surveillance and district health information systems data for decision making, and 4) rapid field investigations in support of district health department priorities.

Prior to FPD, I was Laboratory Branch Chief for CDC-South Africa. In this capacity, I supported and advised the South African National Health Laboratory Service and the National Department of Health on national point-of-care diagnostics policy and guidelines. As an outbreak investigation specialist, I was twice deployed to West Africa in 2015 to work with *Médecins Sans Frontières* (*MSF*; a.k.a., Doctors without Borders) to contain the on-going Ebola outbreak. While there, I specifically led disease surveillance, case investigation and contact tracing activities in affected communities. I also supported and optimized epidemiologic data flow from Ebola Treatment Units to the Ministry of Health.

As a Molecular Biologist, I conducted research into the molecular mechanisms of *Neisseria gonorrhea* adherence and invasion at Rockefeller University, and helped identify a key cell receptor that facilitates NG adherence and invasion. In 2010, I was awarded the Donald C. Mackel Memorial Award by the CDC for my investigation into a fatal laboratory-acquired infection with an attenuated *Yersinia pestis* strain; the Mackel Award is given annually to the CDC Epidemic Intelligence Service Officer that best exemplifies the effective application of a combined epidemiologic and laboratory approach to an investigation.

Dr. Klausner and I have known and collaborated with each other since 2010, mentoring trainees, implementing USAID, CDC and NIH-funded research, and co-authoring publications. Our long-running collaborations will allow us to successfully co-lead our study team, and the implementation of this project. As the Principal Investigator and implementation expert on this project, I will co-lead with Dr. Klausner the oversight, design, implementation, and analysis of this study. I will specifically be responsible for the coordination of all in-country study implementation efforts and quality assurance, and will provide direct oversight for the South African-based study team, including clinic-based research staff who will have direct contact with patient-participants and data managers. My strong knowledge of and relationship with the Tshwane District Department of Health, in my capacities as a Systems Strengthening Technical Advisor and on Dr. Klausner's and my current R21 study, has provided me with key insights and experiences that will allow me to successfully risk manage and implement all aspects of this proposed study.

B. Positions and Honors

Positions and Employment

1995 – 1996 Undergraduate Researcher, Rockefeller University

1999 – 2000	Undergraduate Researcher, Laboratory of Molecular Systematics, Smithsonian Institution
2000 – 2001	Postbaccalaureate Researcher, National Institute of Allergy and Infectious Diseases, U.S. NIH
2002 – 2008	Howard Hughes Medical Institute Fellow, California Institute of Technology
2009 – 2011	Epidemic Intelligence Service (EIS) Officer, Centers for Disease Control and Prevention
2012	Objective Review Panel Member, U.S. President's Emergency Plan for AIDS Relief
2011 – 2012	Chief, Laboratory Branch, U.S. Centers for Disease Control, South Africa
2014 – 2015	Epidemiologist, *Médecins Sans Frontières*, West Africa Ebola Response
2012 – Present	Senior Technical Advisor, Disease Surveillance and Laboratory Systems Strengthening, Foundation for Professional Development
2014 – Present	Head, Research Unit, Foundation for Professional Development
2016 – Present	Member, South African National TB Think Tank
2016 – Present	Member, South African National HIV Think Tank

Awards and Honors

1996	Undergraduate Research Fellow, U.S. Department of Energy
1998	Best Undergraduate Thesis, American Society for Cell Biology
1999	Research Training Award, Smithsonian Institution
2001	McCallum Research Award, California Institute of Technology
2001	Benjamin Rosen Graduate Fellowship, California Institute of Technology
2002	Ford Foundation Fellowship
2002	Howard Hughes Medical Institute Fellow
2010	Donald C. Mackel Award, Centers for Disease Control and Prevention
2011	Remsen Bird Lecture, Occidental College
2017	Global Health Grand Rounds Lecture, Vanderbilt University

C. Contribution to Science

1. Optimizing STI Screening and Testing Programs in South Africa: The burden of bacterial and viral STIs, and their subsequent sequelae, is unacceptably high in South Africa and other low-middle income countries. Moreover, the sub-optimal sensitivity and specificity of current screening protocols (i.e., syndromic management of CT, NG and TV), and poor screening coverage (i.e., HPV/ cervical cancer screening), leave a large number of women undiagnosed and untreated. The impact of this is on-going transmission to sexual partners, increased risk of mother-to-child transmission of HIV, and increased morbidity and mortality, especially among reproductive age women. With the advent of new molecular diagnostic tests and point-of-care test platforms, I have been working to improve access to and implementation of bacterial and viral STIs screening and treatment programs. This work is particularly highlighted by two recent research projects where I serve as PI: 1) Evaluating the acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa; and 2) Pilot Study of STI Screening and Treatment for PMTCT (R21HD084274). Both studies have been conducted in Tshwane District (the proposed study district for the current proposal), allowing me to develop excellent relationships with the local health department, and have key insights into the barriers and facilitators for new test implementation in Tshwane District health clinics.

1. Price CM, Peters RPH, Mudau M, Olivier D, De Vos L, Morikawa E, Kock MM, **Medina-Marino A**, Klausner JD. Prevalence and Detection of *Trichomonas Vaginalis* in Human Immunodeficiency Virus-Infected Pregnant Women. Sex Transm Dis. 2018 May;45(5):332-336. doi: 10.1097/OLQ.0000000000000756. PMID: 29465686

2. Shannon CL, Bristow CC, Hoff N, Wynn A, Nguyen M, **Medina-Marino A**, Klausner JD Acceptability of Rapid Chlamydial, Gonococcal, and Trichomonal Screening and Treatment in Pregnant Women in Six Low-to-Middle Income Countries. Sex Transm Dis. 2018 Mar 9. doi: 10.1097/OLQ.0000000000000832

3. Peters RPH, Mudau M, Liteboho M, de Vos L, Klausner JD, Kock MM, **Medina-Marino A*** Laboratory reproducibility of Xpert® CT/NG and TV testing as performed by nurses at three primary healthcare facilities in South Africa. J Clin Microbiol. 2017 Oct 11. pii:JCM.01430-17. (**Senior/Corresponding Author*)

4. Mudau M, Remco Peters P, De Vos L, Olivier D, Joseph Davey D, Mkhwanazi E, McIntyre JA, Klausner JD, **Medina-Marino A***. High prevalence of asymptomatic sexually transmitted infections among Human

Immunodeficiency Virus (HIV)-Infected pregnant women in a low-income South African community. Int J STD *AIDS* 2017 Aug 11 DOI: 10.1177/0956462417724908 (**Senior/Corresponding Author*)

2. TB Epidemiology, Program Support and Case Finding: Despite health systems strengthening activities aimed at improving the national TB control program, South Africa still bears one of the highest TB burdens in the world. Improving TB surveillance, case finding and retention in care are paramount to improving national TB programmatic indicators, and decreasing the burden of TB throughout the country. Towards this, I have worked closely with a number of health districts around South Africa to evaluate their TB surveillance systems, and to identify the magnitude of cases being missed by the health system. This work is highlighted by the below references. In addition, I was recently awarded an NIH R21 grant (R21EB023679; NIBIB) to investigating the acceptability and feasibility of true home-based TB testing of household contacts using the new, portable point-of-care GeneXpert Omni platform. My team and I will be 1 of only 10 teams, globally, given early access to this new portable TB testing platform to pilot its use in a host of settings. This work may open up an entirely new way of conducting TB case finding, with potential global implications.

1. Kweza PF, van Schalkwyk C, Abraham N, Uys M, Claassens MM, **Medina-Marino A*** Estimating the magnitude of missed pulmonary tuberculosis patients by primary health facilities, South Africa. Int J Tuberc Lung Dis 2018 Mar 1;22(3):264-272. doi: 10.5588/ijtld.17.0491. (**Senior/Corresponding Author*)
2. Mlotshwa M, Smit S, Williams S, Reddy S, **Medina-Marino A*** Evaluating the Electronic Tuberculosis Register Surveillance System in Eden District, Western Cape, South Africa, 2015 Glob Health Action. 2017;10(1):1360560. doi: 10.1080/16549716.2017.1360560. (**Senior/Corresponding Author*)
3. Mlotshwa M, Abraham N, Beery M, Williams S, Smit S, Uys M, Reddy C, **Medina-Marino A***. Risk factors for tuberculosis smear non-conversion in Eden district, Western Cape, South Africa, 2007-2013: a retrospective cohort study. BMC Infect Dis. 2016 Aug 2;16:365. doi: 10.1186/s12879-016-1712-y. PMID: 27484399 (**Senior/Corresponding Author*)
4. *Sweetland AC, Jaramillo E, Wainberg ML, Chowdhary N, Oquendo MA,* ***Medina-Marino A****, Dua T* Tuberculosis: An opportunity to integrate mental health services in primary care in low-resource settings. Lancet Psychiatry 2018 October (In Press)

3. Field Epidemiology, Disease Surveillance and Outbreak Investigations: Identification and rapid response to adverse health events in a population is of particular importance to the prevention and control of infectious diseases. As a trained field epidemiologist, I have honed my skills to perform rapid field investigations and utilize surveillance and routine collected data to inform outbreak containment, program implementation and evaluation. Though my work with *Médecins Sans Frontières* during the 2014-2016 Ebola outbreak in West Africa did not result in any publications, my skills and leadership were recognized by the request for a second deployment with MSF to Liberia in 2015. While there, I specifically led disease surveillance, case investigation and contact tracing activities in affected communities. I also supported and optimized epidemiologic data flow from Ebola Treatment Units to the Ministry of Health.

1. Soyemi K, **Medina-Marino A**, Sinkowitz-Cochran R, Schneider A, Njai R, McDonald M, Glover M, Garcia J, Aiello AE. Disparities among 2009 pandemic influenza A (H1N1) hospital admissions: a mixed methods analysis--Illinois, April-December 2009. PLoS One. 2014;9(4):e84380. Epub 2014/04/30. doi: 10.1371/journal.pone.0084380. PMID: 24776852; PMCID: PMC4002432.
2. **Medina-Marino A**, Reynolds D, Finley C, Hays S, Jones J, Soyemi K. Communication and mass vaccination strategies after pertussis outbreak in rural Amish communities-Illinois, 2009-2010. J Rural Health. 2013;29(4):413-9. Epub 2013/10/04. doi: 10.1111/jrh.12019. PMID: 24088215.
3. Dalhatu IT, **Medina-Marino A***, Olsen SJ, Hwang I, Gubio AB, Ekanem EE, Coker EB, Akpan H, Adedeji AA. Influenza viruses in Nigeria, 2009-2010: results from the first 17 months of a national influenza sentinel surveillance system. J Infect Dis. 2012;206 Suppl 1:S121-8. Epub 2012/11/28. doi: 10.1093/infdis/jis584. PMID: 23169957. *(*Note: This was a co-first authored paper).*
4. Cardemil CV, Cortese MM, **Medina-Marino A**, Jasuja S, Desai R, Leung J, Rodriguez-Hart C, Villarruel G, Howland J, Quaye O, Tam KI, Bowen MD, Parashar UD, Gerber SI, Rotavirus Investigation Team.

Two rotavirus outbreaks caused by genotype G2P[4] at large retirement communities: cohort studies. Ann Intern Med. 2012;157(9):621-31. Epub 2012/11/07. doi: 10.7326/0003-4819-157-9-201211060-00006. PMID: 23128862

4. Molecular Mechanisms of Infectious Disease Pathogenesis: Insights into the pathogenic mechanisms of infectious diseases can be informed by both basic cell biology research and outbreak investigations. Colleagues and I identified the 180-kD carcinoembryonic antigen (CEA) cell surface protein as a receptor and mediator of *Neisseria gonorrhoeae* adherence and invasion into epithelial cells. As an Epidemic Intelligence Service Officer, I led a field investigation into a fatal laboratory-acquired infection with an attenuated strain of *Yersinia pestis*, the causative agent of plague. Our work uncovered the previously unknown risk associated with hereditary hemochromatosis and susceptibility and enhanced virulence of the pgm- KIM D27 strains of *Yersinia pestis.*

1. **Medina-Marino A**, Sheih W-J, Zaki S, Schriefer M, Molins C, Mead P, King B, Metzger K, Soyemi K, Conover C, Gerber S, Jones J, Weaver K, Black S, Ritger K, Centers for Disease Control and Prevention. Fatal laboratory-acquired infection with an attenuated Yersinia pestis Strain--Chicago, Illinois, 2009. MMWR Morb Mortal Wkly Rep. 2011;60(7):201-5. PMID: 21346706.
2. Chen T, Grunert F, **Medina-Marino A**, Gotschlich EC. Several carcinoembryonic antigens (CD66) serve as receptors for gonococcal opacity proteins. J Exp Med. 1997;185(9):1557-64. Epub 1997/05/05. PMID: 9151893; PMCID: PMC2196295.

5. Molecular Phylogenetics: As a Research Fellow in molecular evolution at the Smithsonian Institution, I used molecular sequence data to reconstruct the phylogenetic history of organismal adaptive radiations. Though the work was focused on plants, the techniques and applications behind my work in molecular phylogenetics will allow me to contribute to data analysis and interpretations relating to the molecular epidemiology of *Chlamydia trichomonas* and *Trichomonas vaginalis* that will be a self-funded sub-study emanating from our currently proposed study.

1. Whittall JB, **Medina-Marino A**, Zimmer EA, Hodges SA. Generating single-copy nuclear gene data for a recent adaptive radiation. Mol Phylogenet Evol. 2006;39(1):124-34. Epub 2005/11/30. doi: 10.1016/j.ympev.2005.10.010. PMID: 16314114.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1pEG7AXedlkQM/bibliograpahy/43304628/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R01MH114648 (NIMH/NIH) PIs: Medina-Marino, Bekker 09/01/2017 – 08/31/2022
Title: *Leveraging Community-based Platforms to Improve Access and Adherence to PrEP*
Goals: 1) Assess YW's uptake of PrEP when delivered through large-scale community-based HIV counseling and testing (CBCT) platforms in urban and rural settings in South Africa
2) Evaluate community-based scalable interventions to achieve prevention-effective adherence to PrEP among YW
3) Evaluate the cost per YW initiated on PrEP and provided adherence support through community-based platforms, and the cost-effectiveness per incident HIV infection averted

1U19MH113203 (NIMH/NIH) PIs: Wainberg, Oquendo 05/01/2017 – 04/30/2022
Title: PRIDE SSA- Partnership in Research to Implement and Disseminate Sustainable and Scalable Evidence Based Practices in Sub-Saharan Africa
Goals: 1) In partnership with policy makers, conduct rigorous scale-up research to identify and implement the best task-sharing delivery pathway for community-based mental health care and treatment
2) Train, develop and support a research network in sub-Saharan Africa
3) Develop sub-Saharan Africa in-country formal capacity-building programs in mental health implementation science

4) Establish an administrative structure to robustly support and oversee the scale-up research and capacity building components

Role: Lead data collection implementation and quality assurance processes and procedures, and oversee academic capacity-building component

Recently Completed Research Support

5R21HD084274 (NICHHD/NIH) PIs: Medina-Marino, Klausner 09/23/2015 – 7/31/2018

Title: Pilot Study of STI Screening and Treatment for PMTCT

Goals: 1) Determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit.
2) Describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit.

5R21EB023679 (NIBIB/NIH) PI: Medina-Marino 08/15/2016 – 05/31/2018

Title: Investigating the acceptability and feasibility of home-based TB testing of household contacts using a new, mobile point-of-care technology

Goals: 1) Determine the acceptability and feasibility of using point-of-care technology to perform home-based TB testing of household contacts of TB patients
2) Describe the outcomes of household contacts screened and tested for TB in their home compared to those screened and referred for testing in a health facility

AID-3569023-102-2015-02/03 (USAID) PI: Burke/ Site PI: Medina-Marino 08/01/2015 – 05/31/2018

Title: A randomized study evaluating an intervention integrating economic strengthening and HIV prevention programs for vulnerable youth in South Africa

Goals: 1) Assess whether the integration of an economic strengthening (ES) intervention with an HIV-prevention education intervention improves economic and health outcomes beyond singular interventions;
2) Estimate the resources required at the program level to support the ES and HIV-prevention education interventions; and
3) Describe whether the interventions were perceived as effective in addressing economic and health outcomes and to describe how and why the interventions were perceived as effective or not.

AID-674-A-14-0006 (USAID) PI: Wolvaardt 09/13/2013 – 01/01/2019

Title: Communities Forward- A Comprehensive Community–Based HIV Prevention, Counselling and Testing Program for Reduced HIV Incidence

Goals: To conduct evaluations and implementation science activities in conjunction with implement of community-based HIV counselling and testing activities in 13 high burden districts throughout South Africa.

Role: Head of all research activities associated with CoAg

AID-674-A-12-00017 (USAID) PI: Wolvaardt 10/31/2012 – 12/31/2018

Title: Strengthening systems for better HIV/TB patient outcomes

Goals: To conduct pragmatic evaluations and implementation science activities in conjunction with the implementation of health systems strengthening strategies to improve the quality of service delivery.

Role: Head of all research activities associated with CoAg

Projects: 1) Estimating the magnitude of TB cases missed by the health system
2) Factors affecting presentation for first antenatal care visit in Tlokwe sub-district, Northwest Province and Capricorn District, Limpopo Province, South Africa
3) Evaluating the acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa
4) In-clinic laboratory services assessment in PHCs and CHCs in Tshwane, Nkangela, Vhembe and Capricorn Districts

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Taylor, Christopher Michael

eRA COMMONS USER NAME (credential, e.g., agency login): CHRISTAYLOR

POSITION TITLE: Associate Professor of Microbiology, Immunology, and Parasitology
Director of Bioinformatics, Biostatistics & Computational Biology

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

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Mary Washington College, Fredericksburg, VA	B.S.	05/2000	Computer Science and Math
University of Virginia, Charlottesville, VA	M.S.	08/2002	Computer Science
University of Virginia, Charlottesville, VA	Ph.D.	05/2008	Computer Science

A. Personal Statement

I am a computer scientist and mathematician by training. I began studying computational biology in graduate school where I developed algorithms for analysis and visualization of human genome tiling array data [1]. I have been working with high-throughput DNA sequencing data for over a decade now and my lab has a primary focus on the development of analysis and visualization methods for high-throughput sequencing data of microbial communities. We developed a novel method called Oligotyping for looking in great detail at 16S rDNA sequences for subtle nucleotide variations that can reveal community composition down to a strain level [2]. This was one of the first methods for analysis of 16S rDNA data that did not rely on clustering of sequences into Operational Taxonomic Units. We applied this method in a paired sexual partner study of vaginal swabs from women and urethral swabs from their male sexual partners and our Oligotyping method showed a strong correlation between *Gardnerella vaginalis* sequences shared across sexual partners [2]. In a follow-up study, we extended this analysis to the entire vaginal microbiome and showed that the vaginal microbiota of women with bacterial vaginosis [BV] is more similar to her male sexual partner's penile skin and urethral microbiota supporting the hypothesis of sexual transmission of BV associated bacteria [3]. We have recently been following a cohort of women enrolled in a prospective study where we have sequenced and analyzed daily vaginal samples leading up to diagnosis of BV and shown that several BV associated bacteria rise in abundance prior to onset of BV and may play a crucial role in the etiology of the disease [4]. My lab has also recently been awarded a multi-PI R01 to study the relationship between the vaginal microbiota and natural clearance of Chlamydia infection. As an expert in the analysis and visualization of microbial communities with specific emphasis on the vaginal microbiota in STIs, I am ideally positioned to lead the sequencing, analysis, and data visualization aspects of this project.

1. Karnani N, **Taylor CM**, Dutta A. Microarray analysis of DNA replication timing. Methods Mol Biol. 2009;556:191-203. PMID: 15499007. PMCID: PMC4201590.
2. Eren AM, Zozaya M, **Taylor CM**, Dowd SE, Martin DH, Ferris MJ. Exploring the diversity of Gardnerella vaginalis in the genitourinary tract microbiota of monogamous couples through subtle nucleotide variation. PLoS One. 2011;6(10):e26732. PMID: 22046340; PMCID: PMC3201972.
3. Zozaya M, Ferris MJ, Siren JD, Lillis R, Myers L, Nsuami MJ, Eren AM, Brown J, **Taylor CM**, Martin DH. Bacterial communities in penile skin, male urethra, and vaginas of heterosexual couples with and without bacterial vaginosis. Microbiome. 2016 Apr 19:4:16. PMID: 27090518; PMCID: PMC4835890.
4. Muzny CA, Blanchard E, **Taylor CM**, Aaron KJ, Talluri R, Griswold ME, Redden DT, Luo M, Welsh DA, Van Der Pol WJ, Lefkowitz EJ, Martin DH, Schwebke JR. Identification of Key Bacteria Involved in the Induction of Incident Bacterial Vaginosis: A Prospective Study. J Infect Dis. 2018 Aug 14;218(6):966-978. PMID: 29718358; PMCID: PMC6093354.

B. Positions and Honors

Positions and Employment

2008-2012 Assistant Professor of Computer Science, University of New Orleans, New Orleans, LA
2012-Present Associate Professor of Microbiology, Immunology & Parasitology, Louisiana State University Health Sciences Center, New Orleans, LA
2016-Present Director of Bioinformatics, Biostatistics & Computational Biology Core for the Louisiana Biomedical Research Network, Baton Rouge, LA

Other Experience and Professional Memberships

2008 Session Chair of Pattern Recognition in Bioinformatics (PRIB 2008), Melbourne, AUS
2009 Local Arrangements Chair of High-Performance Graphics (HPG 2009), New Orleans, LA
2010-2011 Coach of ACM South Central USA Regional Programming Contest Team
2013 Panelist for LBRN Computational Biology Workshop, New Orleans, LA
2013 Session Chair for ASM TX/SC Branch Meeting, New Orleans, LA
2015 Session Chair for 3rd Microbiome R&D and Business Collaboration Forum, San Diego, CA
2015 Scientific Committee for the 3rd Annual LA Conference on Bioinformatics, Baton Rouge, LA
2017 Organizational Co-Chair for the 5th Annual LA Conference on Bioinformatics, New Orleans, LA
2018 Organizational Co-Chair for the 6th Annual LA Conference on Bioinformatics, Baton Rouge, LA

Honors

2009 Best Presentation Award for Invited Talk at Louisiana State University Pediatrics Day
2015 Winner of Illumina's MiSeq My Focus Contest and Recipient of $5,000 in Sequencing Reagents

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C. Contribution to Science

1. My early work in the field of computational biology involved the analysis of data from Genome Tiling Microarrays. After the full human genome sequence was released, the NIH initiated the ENCODE project with the purpose of studying and annotating all of the functional elements in the human genome. I joined Dr. Anindya Dutta's lab in 2003 which was funded on an ENCODE pilot project to study the timing of DNA replication in the human genome. I used my skills in computer science and mathematics to develop a method for generating a continuous profile of DNA replication timing from discrete pools of replicated DNA that were hybridized to genome tiling microarrays. I also proposed a method for finding origins of replication and discovering regions of the genome where alleles replicated asynchronously. This approach was presented at Pattern Recognition in Bioinformatics 2008 in Melbourne, Australia and later published as part of an invited chapter for Methods in Molecular Biology in 2009 [a]. During this time, I was also the lead analyst for replication and a member of the Integrated Analysis and Manuscript Preparation group for the ENCODE Nature publication [b]. We also published other aspects of this work in Genome Research [c] and Molecular Biology of the Cell [d]. This period of my research career was critical at introducing me to the analysis of genomic data as I developed my own algorithms for interrogating genome tiling microarrays, laying the groundwork for my future work in analysis and visualization of high-throughput sequencing data.

    a. Karnani N, **Taylor CM**, Dutta A. Microarray analysis of DNA replication timing. Methods Mol Biol. 2009;556:191-203. PMID: 15499007. PMCID: PMC4201590.
    b. ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, Dutta A, Guigó R, Gingeras TR, Margulies EH, Weng Z, Snyder M, Dermitzakis ET, Thurman RE, Kuehn MS, **Taylor CM** et al. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature. 2007 Jun 14;447(7146),799-816. PMID: 17571346. PMCID: PMC2212820.
    c. Karnani N, **Taylor C**, Malhotra A, Dutta A. Pan-S replication patterns and chromosomal domains defined by genome-tiling arrays of ENCODE genomic areas. Genome Research. 2007 Jun;17(6), 865-876. PMID: 17568004. PMCID: PMC1891345.
    d. Karnani N, **Taylor CM**, Malhotra A, Dutta A. Genomic study of replication initiation in human chromosomes reveals the influence of transcription regulation and chromatin structure on origin selection. Molecular Biology of the Cell. 2010 Feb 1; 21(3), 393-404. PMID: 19955211. PMCID: PMC2814785.

2. In 2009 I began collaborating with a virologist and my laboratory developed RNA Sequencing analysis tools that would interrogate the reads that didn't map to the host genome which were typically discarded in other analysis pipelines at the time. We followed these reads by mapping them to other potential databases in succession and assembled transcripts to discover what exogenous agents may be found within RNA-Sequencing data of a host. This software system was called PARSES: Pipeline for Analysis of RNA-Seq Exogenous Sequences [a]. Using this approach, we discovered murine leukemia virus in an EBV positive human B-cell line [a]. This technology was then integrated into a full-featured software system called RNA CoMPASS: RNA Comprehensive Multi-Processor Analysis System for Sequencing which performed both the typical endogenous analysis and our exogenous analysis from PARSES in tandem and was distributable over a cluster to parallelize the computation [b]. This process of dual analysis of RNA-Sequencing data led to many interesting findings [c,d] and established a strong collaboration with Erik Flemington's lab. We also helped Erik to establish the Cancer Crusaders Bioinformatics Lab which was an initial testing ground for our model of collaborative research.

    a. Lin Z, Puetter A, Coco J, Xu G, Strong MJ, Wang X, Fewell C, Baddoo M, **Taylor C**, Flemington EK. Detection of murine leukemia virus in the Epstein-Barr virus-positive human B-cell line JY, using a computational RNA-Seq-based exogenous agent detection pipeline, PARSES. J Virol. 2012;86(6):2970-7. PMID: 22238296; PMCID: PMC3302299.
    b. Xu G, Strong MJ, Lacey MR, Baribault C, Flemington EK, **Taylor CM**. RNA CoMPASS: a dual approach for pathogen and host transcriptome analysis of RNA-seq datasets. PLoS One. 2014 Feb 25;9(2):e89445. PMID: 24586784; PMCID: PMC3934900.
    c. Strong MJ, Xu G, Coco J, Baribault C, Vinay DS, Lacey MR, Strong AL, Lehman TA, Seddon MB, Lin Z, Concha M, Baddoo M, Ferris M, Swan KF, Sullivan DE, Burow ME, **Taylor CM**, Flemington EK. Differences in gastric carcinoma microenvironment stratify according to EBV infection intensity; implications for possible immune adjuvant therapy. PLoS Pathog. 2013;9(5):e1003341. PMID: 23671415; PMCID: PMC3649992.
    d. Strong MJ, O'Grady T, Lin Z, Xu G, Baddoo M, Parsons C, Zhang K, **Taylor CM**, Flemington EK. Epstein-Barr virus and human herpesvirus 6 detection in a non-Hodgkin's diffuse large B-cell lymphoma cohort by using RNA-seq. J Virol. 2013 Dec;87(23):13059-62. PMID: 24049168; PMCID: PMC3838131.

3. The major focus of my current research began in 2010 with analysis of microbial communities through sequencing of 16S rRNA. My group developed a software framework for analysis called Viamics [a]. This system was intended to be easy to use for biologists who had limited experience with command line tools such as Mothur. We also developed a novel method for looking at subtle nucleotide variation in the 16S reads called oligotyping [b]. This method allowed for analysis of 16S data to sub-species level and was applied to the genitourinary tract microbiota in monogamous couples. We were able to see strong enough correlations between oligotypes of gardnerella vaginalis in a woman's vaginal microbiota and her male sexual partner's penile skin microbiota that we were able to predict which males and females in our study were sexual partners with a high degree of accuracy. We published a follow up study to [b] where we applied the oligotyping method to additional couples from the paired sexual partner cohort [c] and recently published an analysis of daily vaginal sampling of women prior to diagnosis of bacterial vaginosis.

    a. Murat Eren A, Ferris MJ, **Taylor CM**. A framework for analysis of metagenomic sequencing data. Pac Symp Biocomput. 2011:131-41. PMID: 21121041. NIH public access N/A-not NIH funded.
    b. Eren AM, Zozaya M, **Taylor CM**, Dowd SE, Martin DH, Ferris MJ. Exploring the diversity of Gardnerella vaginalis in the genitourinary tract microbiota of monogamous couples through subtle nucleotide variation. PLoS One. 2011;6(10):e26732. PMID: 22046340; PMCID: PMC3201972.
    c. Zozaya M, Ferris MJ, Siren JD, Lillis R, Myers L, Nsuami MJ, Eren AM, Brown J, **Taylor CM**, Martin DH. Bacterial communities in penile skin, male urethra, and vaginas of heterosexual couples with and without bacterial vaginosis. Microbiome. 2016 Apr 19:4:16. PMID: 27090518; PMCID: PMC4835890.
    d. Muzny CA, Blanchard E, **Taylor CM**, Aaron KJ, Talluri R, Griswold ME, Redden DT, Luo M, Welsh DA, Van Der Pol WJ, Lefkowitz EJ, Martin DH, Schwebke JR. Identification of Key Bacteria Involved in the Induction of Incident Bacterial Vaginosis: A Prospective Study. J Infect Dis. 2018 Aug 14;218(6):966-978. PMID: 29718358; PMCID: PMC6093354.

4. Our early work in the vaginal microbiome and studies of Bacterial Vaginosis led to an interest in studying the newborn infant gut microbiota due to the intimate association between a mother's vaginal microbiota and the newborn infant's gut microbiota. We developed a collaboration with a clinician (Duna Penn) who was collecting fecal samples from premature infants and sequenced the gut microbiota of these infants. We found an association between H2 receptor blockers and the fecal microbiota and our article appeared on the cover of the issue of the Journal of Pediatric Gastroenterology Nutrition in which it appeared [a]. This study was followed up with an investigation of the development of necrotizing enterocolitis in premature infants. We found that both overall bacterial diversity and Clostridia abundance decreased in the infant gut microbiome with increasing severity of necrotizing enterocolitis [b]. We have recently reported a similar study describing changes in the gut microbiome of pediatric patients with end stage renal disease [c]. This work has all seeded an interest in understanding the drivers of initial colonization of the infant gut and we have recently secured funding to perform environmental sampling of Neonatal Intensive Care Units and the gut microbiome of newborn infants housed within them to look for associations between environmental bacteria and colonizers of the newborn infant gut.

    a. Gupta RW, Tran L, Norori J, Ferris MJ, Eren AM, **Taylor CM**, Dowd SE, Penn D. Histamine-2 receptor blockers alter the fecal microbiota in premature infants. J Pediatr Gastroenterol Nutr. 2013 Apr;56(4):397-400. PMID: 23254444. NIH public access N/A-not NIH funded.
    b. McMurtry VE, Gupta RW, Tran L, Blanchard EE 4th, Penn D, **Taylor CM**, Ferris MJ. Bacterial diversity and Clostridia abundance decrease with increasing severity of necrotizing enterocolitis. Microbiome. 2015 Mar 23;3:11. PMID: 25810906; PMCID: PMC4373520.
    c. Crespo-Salgado J, Vehaskari VM, Stewart T, Ferris M, Zhang Q, Wang G, Blanchard EE, **Taylor CM**, Kallash M, Greenbaum LA, Aviles DH. Intestinal microbiota in pediatric patients with end stage renal disease: a Midwest Pediatric Nephrology Consortium study. Microbiome. 2016 Sep 17;4(1):50. PMID: 27640125; PMCID: PMC5027112.

5. Because of our interest in human health and the difficulty and ethical issues associated with performing mechanistic studies in human patients, we have embarked on a large number of model organism studies investigating the association of gut microbiota with obesity and the ability to modulate the gut microbiota. We began with a study looking at the influence of a series of botanical extracts on the mucosal and luminal microbiota in diet-induced obese mice [a]. We found that the botanical supplements differentially affected the mucosal and luminal microbiota and hence that it was important to include both types of samples in future studies. Once this model was developed, we performed an adoptive transfer of gut microbiota in mice and showed that we could induce neurobehavioral changes in the absence of obesity by transplanting microbiota from obese mice into lean mice that are maintained on a standard chow diet [b]. We have since investigated the host response to infection with Pneumocystis pneumonia and how it changes based on differences in the intestinal microbiota [c]. We have recently used a probiotic, Lactobacillus reuteri, to inhibit immune deficiencies by modulating the gut microbiota in mice [d]. These studies have all established the models and ability for us to modulate the gut microbiota in mice via antibiotics, probiotics, botanicals and adoptive transfer in order to mechanistically study changes in response to pathogen challenges. Ultimately, we aim to translate these findings to bear on the human condition.

    a. Wicks S, **Taylor CM**, Luo M, Blanchard IV E, Ribnicky D, Cefalu WT, Mynatt RL, Welsh DA. Artemisia supplementation differentially affects the mucosal and luminal ileal microbiota of diet-induced obese mice. Nutrition. 2014 Jul-Aug;30(7-8 Suppl):S26-30. PMID: 24985102. PMCID: PMC4197130.
    b. Bruce-Keller AJ, Salbaum JM, Luo M, Blanchard E 4th, **Taylor CM**, Welsh DA, Berthoud HR. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. Biol Psychiatry. 2015 Apr 1;77(7):607-15. PMID: 25173628; PMCID: PMC4297748.
    c. Samuelson DR, Charles TP, de la Rua NM, **Taylor CM**, Blanchard EE, Luo M, Shellito JE, Welsh DA. Analysis of the intestinal microbial community and inferred functional capacities during the host response to Pneumocystis pneumonia. Exp Lung Res. 2016 Oct – Dec;42(8-10):425-439. PMID: 27925857; PMCID: PMC5304582.
    d. He B, Hoang TK, Wang T, Ferris M, **Taylor CM**, Tian X, Luo M, Tran DQ, Zhou J, Tatevian N, Luo F, Molina JG, Blackburn MR, Gomez TH, Roos S, Rhoads JM, Liu Y. Resetting microbiota by Lactobacillus reuteri inhibits T reg deficiency-induced autoimmunity via adenosine A2A receptors. J Exp Med. 2017 Jan;214(1):107-123. PMID: 27994068; PMCID: PMC5206500.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/christopher.taylor.1/bibliography/43101263/public/?sort=date&direction=ascending

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D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R01AI118860-01A1 Taylor/Quayle/Aiyar (MPIs) 08/08/17 – 07/31/21
NIH/NIAID
Consequences of vaginal microbiota on IFN-gamma-mediated clearance of Chlamydia trachomatis
The goal of this award is to characterize the vaginal microbiota that is associated with spontaneous clearance of Chlamydia infection. My role is as multi-principal-investigator leading the sequencing and bioinformatics analysis of the vaginal microbiome data.
Role: Multi-Principal-Investigator

1UH2AA026226-01 Welsh (PI) 09/15/17 – 08/31/19
NIH/NIAID
Precision Medicine Approaches for Alcohol and HIV-associated Dysbiosis, Immune Activation and Cardiometabolic Syndrome
The goal of this project is to assess the dysbiosis of microbiota caused by alcohol usage in an HIV-positive population and to investigate possible personalized approaches to treating the dysbiosis.
Role: Co-Investigator

P20GM103424 Kousoulas (PI) 05/01/16 – 04/30/20
NIH/NIGMS
Louisiana Biomedical Research Network
The goal of this funding is to unite the LSU system bioinformatics, biostatistics and computational biology resources. My role is as co-investigator and director of the bioinformatics, biostatistics and computational biology core.
Role: Co-Investigator

U54-TR-001368-01 Kimberly (PI) 09/01/15 – 08/31/19
NIH/NCATS
UAB Center for Clinical and Translational Science (CCTS)
The goal of this center is to promote clinical and translational science across the southern region. UAB, LSU, and Tulane are members of the CCTS. My role in this project is as co-investigator and bioinformatics expert.
Role: Co-Investigator

Recently Completed Research Support

Clinical Research Enhancement Gupta (PI) 01/01/17 – 12/31/18
LSU School of Medicine Clinical Research Enhancement Program
The NICU Microbiome and Gastrointestinal Bacterial Colonization in the Hospitalized Premature Infant: Effect of Antibiotics
The goal of this project is to understand the interactions between microbes in the Neonatal Intensive Care Unit and premature infants undergoing antibiotic treatment using high-throughput 16S rRNA sequencing of microbial communities. My role in this project is as co-investigator directing the sequencing and bioinformatics.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Cleary, Susan May

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Professor in Health Economics

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Rhodes University, Grahamstown, South Africa	BA	12/1996	English and Economics
University of Cape Town, South Africa	BA Honours	12/1999	Economics
University of Cape Town, South Africa	Masters	12/2001	Economics
University of Cape Town, South Africa	PhD	12/2007	Health Economics

A. Personal Statement

Susan Cleary, PhD, is an Associate Professor in Health Economics in the School of Public Health and Family Medicine at the University of Cape Town. She has more than 15 years' experience in cost-effectiveness analysis and decision analytic modeling. She (co)authored the first CEAs of HIV-treatment in South Africa from clinical trials, routine public primary health care settings and private practice. Since then, Dr. Cleary has conducted and supervised CEAs across a diverse set of disease and programme areas including cryptococcal antigen screening, HPV vaccination, interventions to improve quality of care for children and models of care for antiretroviral treatment, amongst others. Current projects include the cost-effectiveness of GeneXpert for TB diagnosis and behavioural interventions for mental illness in patients with HIV or Diabetes. She has given extensive policy input over the years, including (co-)leading the economics and financing components of the South African National Strategic Plans for HIV, STIs and TB covering the periods 2007-2011 and 2012-2016.

Dr. Cleary has considerable experience assessing the affordability and accessibility of study interventions from the patient perspective. For this project, she will oversee all cost/cost-effectiveness related activities (Aim 2).

B. Positions and Honors

2001-2004: Junior Researcher, Health Economics Unit, School of Public Health and Family Medicine, UCT
2004-2007: Researcher, Health Economics Unit, School of Public Health and Family Medicine, UCT
2008-2010: Senior Lecturer, Health Economics Unit, School of Public Health and Family Medicine, UCT
2007-2011: Director, Health Economics Unit, School of Public Health and Family Medicine, UCT
2011 to date: Associate Professor, Health Economics Unit, School of Public Health and Family Medicine, UCT

C. Contributions to Science

1. Cost-effectiveness of HIV-treatment

When I started working as a health economist in 2001, the HIV-epidemic was arguably the most critical challenge facing the South African health system. At this stage, there were no data available on the cost-effectiveness of HIV-treatment within our setting. To fill this gap, I collected primary data from antiretroviral services, HIV wellness services and within hospitals and developed Markov modeling expertise in order to

ultimately assess the full costs of HIV care and the cost-effectiveness of Antiretroviral Treatment (ART). This work has continued over time to include evaluations of alternative models of care for ART and approaches to managing common opportunistic infections, amongst others.

1. Jarvis JN, Harrison TS, Lawn SD, Meintjes G, Wood R, Cleary S. Cost effectiveness of cryptococcal antigen screening as a strategy to prevent HIV-associated cryptococcal meningitis in South Africa. *PLoS One*. 2013;8(7):e69288. doi:10.1371/journal.pone.0069288. PMID: 23894442 PMCID: PMC3716603.
2. Bango F, Ashmore J, Wilkinson L, van Cutsem G, Cleary S. Adherence clubs for long-term provision of antiretroviral therapy: cost-effectiveness and access analysis from Khayelitsha, South Africa. *Trop Med Int Heal*. 2016;21(9):1115-1123. doi:10.1111/tmi.12736. PMID: 27300077.
3. Cleary SM, McIntyre D, Boulle AM. Assessing efficiency and costs of scaling up HIV treatment. *AIDS*. 2008;22 Suppl 1:S35-42. doi:10.1097/01.aids.0000327621.24232.71. PMID: 18664951.
4. Cleary SM, McIntyre D, Boulle AM. The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa--a primary data analysis. *Cost Eff Resour Alloc*. 2006;4:20. doi:10.1186/1478-7547-4-20. PMID: 17147833 PMCID: PMC1770938.

2. Affordability of HIV-treatment

In addition to understanding cost-effectiveness, it was essential to understand the affordability of HIV-related treatment, given the large and new burden of disease, the relatively high cost of treatment, and the potentially long duration of ART. I therefore developed cost modeling expertise, which enables me to provide extensive policy input, including chairing or co-chairing the costing and financing components of the government's National Strategic Plans for HIV/AIDS and STIs covering the periods 2007-2011 and 2012-2016. In addition, I was part of a team that developed costing models that were used by UNAIDS, WHO and low and middle income countries seeking to cost their national strategic plans. From a conceptual perspective, I developed a mathematical programming approach that is capable of simultaneously assessing cost-effectiveness and affordability.

1. Cleary S, McIntyre D. Financing equitable access to antiretroviral treatment in South Africa. *BMC Health Serv Res*. 2010;10(Suppl 1):S2. doi: 10.1186/1472-6963-10-S1-S2. PMID: 20594368 PMCID: PMC2895746.
2. Cleary S, Mooney G, McIntyre D. Equity and efficiency in HIV-treatment in South Africa: the contribution of mathematical programming to priority setting. *Health Econ*. 2010;19(10):1166-1180. doi: 10.1002/hec.1542. PMID: 19725025.
3. Cleary SM, Mcintyre D. Affordability - the forgotten criterion in health-care priority setting. *Health Econ*. 2009;18:373-375. doi:10.1002/hec. PMID: 19267322.

3. Costs and cost-effectiveness of HIV-treatment in other populations

While my initial passion was to work towards the provision of HIV-treatment to South Africans dependent on our public health system, I also contributed towards the understanding of costs and cost-effectiveness within the South African private health system, both on its own, and in comparison to public sector care. Similarly, I supported work related to the economic evaluation of HIV-treated within other low and middle income settings.

1. Leisegang R, Maartens G, Hislop M, Sargent J, Darkoh E, Cleary S. A novel Markov model projecting costs and outcomes of providing antiretroviral therapy to public patients in private practices versus public clinics in South Africa. *PLoS One*. 2013;8(2):e53570. doi:10.1371/journal.pone.0053570. PMID: 23405073 PMCID: PMC3566152.
2. Nachega JB, Leisegang R, Bishai D, et al. Association of Antiretroviral Therapy Adherence and Health Care Costs. *Ann Intern Med*. 2010;152:18-25. doi: 10.7326/0003-4819-152-1-201001050-00006. PMID: 20048268.
3. Leisegang R, Cleary S, Hislop M, et al. Early and Late Direct Costs in a Southern African Antiretroviral Treatment Programme: A Retrospective Cohort Analysis. Rosen S, ed. *PLoS Med*. 2009;6(12):11. doi: 10.1371/journal.pmed.1000189. PMID: 19956658 PMCID: PMC2777319.

4. Jouquet G, Bygrave H, Kranzer K, et al. Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource-limited setting in rural Lesotho. *J Acquir Immune Defic Syndr*. 2011;58(3):e68-74. doi:10.1097/QAI.0b013e31822a9f8d. PMID: 21765366.

4. The patient perspective within economic evaluation

While the abovementioned work on the costs and affordability of HIV-treatment and other health care interventions is key to understanding health systems efficiency and the financing of interventions at scale, I also have a keen interest in understanding the patient perspective in accessing needed interventions. To this end, I have been involved in multiple studies investigating patient access barriers to care, including barriers related to affordability, availability and the acceptability of the health service. This, in addition to the work on efficiency, provides me with insight into the key barriers that patients experience when accessing care, which is essential to consider when designing the implementation of new programmes.

1. Cleary SM, Birch S, Moshabela M, Schneider H. Unequal access to ART: exploratory results from rural and urban case studies of ART use. *Sex Transm Infect*. 2012;88(2):141-146. doi:10.1136/sextrans-2011-050136. PMID: 22345029.
2. Moshabela M, Schneider H, Silal SP, Cleary SM. Factors associated with patterns of plural healthcare utilization among patients taking antiretroviral therapy in rural and urban South Africa: a cross-sectional study. *BMC Health Serv Res*. 2012;12(1):182. doi:10.1186/1472-6963-12-182. PMID: 22747971.
3. Cleary S, Birch S, Chimbindi N, Silal S, Mcintyre D. Investigating the affordability of key health services in South Africa. *Soc Sci Med*. 2013;80:37-46. PMID: 23415590.
4. Foster N, Vassall A, Cleary S, Cunnama L, Churchyard G, Sinanovic E. The economic burden of TB diagnosis and treatment in South Africa. *Soc Sci Med*. 2015;130:42-50. doi:10.1016/j.socscimed.2015.01.046. PMID: 25681713.

5. Costing inpatient care

A final area of expertise that is of relevance to this grant is my work on assessing the costs of inpatient care. Without an electronic patient information system, costing inpatient care in South African public hospitals is challenging and time consuming. However, these estimates are essential in that new technologies often avert inpatient care, making them relatively more cost-effective or even cost saving.

1. Pepper D, Burch V, Levitt N, Cleary S. Hyperglycaemic emergency admissions to a secondary-level hospital – an unnecessary financial burden. S Afr Med J. 2007;12(2):56–60.
2. Cleary, S., Boulle, A., Castillo-Riquelme, M. & McIntyre, D. The burden of HIV/AIDS in the public healthcare system. South Afr. J. Econ. 76, 3–14 (2008). No PMID
3. de Cherif TKS, Schoeman JH, Cleary S, Meintjes G a, Rebe K, Maartens G. Early severe morbidity and resource utilization in South African adults on antiretroviral therapy. BMC Infect Dis. 2009 Dec 15;9:205. doi: 10.1186/1471-2334-9-20. PMID: 20003472 PMCID: PMC2803481.
4. Kevany S, Meintjes G, Rebe K, Maartens G, Cleary S. Clinical and financial burdens of secondary level care in a public sector antiretroviral roll-out setting (G. F. Jooste Hospital). South African Med J SuidAfrikaanse Tydskr vir Geneeskd [Internet]. 2009;99(5):320–5. PMID: 19588792

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing research projects

European & Developing Countries Clinical Trials Partnership PI Giaquinto 1/1/2019 – 12/31/2023
<u>Impact of duration of antibiotic therapy and of oral step-down to amoxicillin or co-amoxiclav on effectiveness, safety and selection of antimicrobial resistance in severe and very severe childhood community-acquired pneumonia (CAP): a randomised controlled trial (PediCAP Trial)</u>
Goal: To understand the effectiveness and cost-effectiveness of alternative antiobiotic prescribing practices on pneumonia outcomes in children
Role: Co-investigator

SA and UK Medical Research Councils PIs Cleary and Jacobs 1/1/2019 – 12/31/2021
The longer term, average and distributional effects of mental health interventions and the causal impact of mental illness on economic outcomes (MIND-ECON)
Goal: To understand the longer-term economic outcomes of the mental health interventions implemented within Project MIND (see below)
Role: Co-Principal Investigator

Wellcome Trust PI Sorsdahl and Myers 01/01/2015 – 12/31/2019
Strengthening South Africa's health system through integrating treatment for mental illness into chronic disease care (Project MIND)
Goal: To understand the effectiveness and cost-effectiveness of models of care and task shifting for mental illness within chronic disease care.
Role: Co-investigator

Completed research projects

United Kingdom DFID RDs Gilson and Hanson 01/01/2011 – 12/31/2018
Responsive and Resilient Health Systems (RESYST)
Goal: An eight year research programme consortium addressing issues of financing, human resources and governance in Africa and Asia.
Role: Management team member

Atlantic Philanthropies PI Gilson and Lehman 01/01/2010 – 12/31/2017
District Innovation and Action Learning for Health Systems (DIALHS)
Goal: An action-learning project supporting district health system development in South Africa.
Role: Co-investigator

Doris Duke Charitable Foundation PI Gilson 01/01/2013 – 12/31/2017
Implementing large-scale health system strengthening intervention: experience from the DDCF's African health Initiative
Goal: A four-year programme of work to understand the factors influencing implementation practice in large-scale health system strengthening projects.
Role: Co-investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Robert Clive Pattinson, M.D.

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Director, MRC Maternal and Infant Health Care Strategies Research Unit

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the Witwatersrand Johannesburg, South Africa	BSc	06/1973	Microanatomy, Biochemistry
University of the Witwatersrand	MB BCh	06/1977	
University of Stellenbosch, Western Cape, Africa	M.Med	06/1985	Obstetrics/Gynecology
South African College of Obstetricians and Gynecologists	FCOG (SA)	06/1985	Obstetrics/Gynecology
Royal College of Obstetricians/Gynecologists London, England	M.D.	06/1992	Doppler Velocimetry
Fellow Royal College Obstetricans Gynaecologists	FRCOG	06/2008	Obstetrics/gynaecology

A. Personal Statement

Professor Bob Pattinson is the director of the South African Medical Research Council's Maternal and Infant Health Care Strategies Research Unit, clinical Head of the Department of Obstetrics and Gynaecology at the University of Pretoria, and an internationally recognized expert in perinatology. He serves on the National Committee for the Confidential Enquiries into Maternal Deaths and the National Perinatal Morbidity and Mortality Committee in South Africa and compiled and edited their reports. He also is responsible for the perinatal care and child health care surveys in South Africa. His main research interests are in obstetrics, medical audits, health systems and effective methods of outreach. His main research focus is on determining the most effective means of implementing new health care strategies and improving current programmes, in other words how to effectively complete the audit cycle. Recently the scale-up of the Essential Steps in Managing Obstetric Emergencies (ESMOE) and Emergency Obstetric Simulation Training (EOST) programme has been completed. This programme demonstrated a 29.3% reduction in maternal mortality before and after its implementation in 12 districts in South Africa. Current clinical research is focusing on predicting and preventing stillbirths.

Dr. Pattinson also served as chairperson of WHO's trial Data Management Committee for Active Management of the Third Stage of Labour from 2008 until 2011. For this study he will oversee the collection of specimens from mother-infant pairs admitted to hospital during and after delivery, the abstraction of medical records and discharge summaries for birth and pregnancy outcomes, and support data analysis and manuscript development relating to adverse pregnancy and birth outcomes.

a. **Pattinson RC**, Hulsbergen MH, Van Hoorick L. The effect of maternal HIV infection on maternal conditions and perinatal deaths in southwest Tshwane. Facts Views Vis Obgyn 2010, 2(4): 227-31.

b. **Pattinson RC**, Kerber K, Waiswa P, Day LT, Mussell F, Asiruddin SK, Blencowe H, Lawn JE. Perinatal mortality audit: Counting, accountability and overcoming challenges in scaling up in low- and middle-income countries. Int J Gynaecol Obstet. 2009 Oct;107 Suppl 1:S113-21, S121-2. doi: 10.1016/j.ijgo.2009.07.011

c. South Africa Every Death Counts Writing Group, Bradshaw D, Chopra M, Kerber K, Lawn JE, Bamford L, Moodley J, **Pattinson R**, Patrick M, Stephen C, Velaphi S. Every death counts: use of mortality audit data for decision making to save the lives of mothers, babies and children in South Africa. Lancet. 2008 Apr 12;371(9620):1294-304. doi: 10.1016/S0140-6736(08)60564-4.

d. Lawn JE, Lee AC, Kinney M, Sibley L, Carlo WA, Paul VK, **Pattinson RC**, Darmstadt GL. Two million intrapartum stillbirths and neonatal deaths: where, why, and what can we do? Int J Gynaecol Obstet. 2009 Oct;107 Suppl 1:S5-18, S19. doi: 10.1016/j.ijgo.2009.07.016.

B. Positions and Honors

Positions and Employment

1981 – 1985	Clinical Assistant, Department Obstetrics & Gynecology, Stellenbosch University Tygerberg Hospital, Parawvallei, RSA
1985 – 1988	Consultant, Department Obstetrics & Gynecology, Stellenbosch University
1988 – 1991	Senior Consultant, Department Obstetrics & Gynecology, Stellenbosch University
1991 – 1992	Principal Consultant, Department Obstetrics & Gynecology, Kalafong Hospital and Pretoria University
1991 -	Professor and Clinical Head, Department Obstetrics and Gynecology, Pretoria University and Chief Specialist, Kalafong Hospital
1997 -	Director, Maternal and Infant Health Care Strategies Research Unit

Other Experiences and Professional Memberships

1992 – 1997	Ethics Committee of the University of Pretoria Medical School
1993 -	School of Primary Health Care, University of Pretoria: member of the management board
1994 – 1996	Chairperson, Maternal and Child Health Care and Nutrition Task Group, Pretoria Region, Gauteng Provincial Administration
1995 – 1999	Member Academic Advisory Group to Dr C Marshall, Director Maternal and Child Health and Nutrition, Gauteng Provincial Administration
1995 – 2000	Executive Member Priorities in Perinatal Care Association,
1995 – 2001	Chairperson - “Pregnancy, neonatology and child growth and development” block for new curriculum, Faculty of Medicine, University of Pretoria,
1997-1999	Chairman: Maternal and Fetal Society of South Africa –
1997 -	Member National Committee for Confidential Enquiries into Maternal Deaths and Editor or all reports
1999 -	Member South African College of Medicine Committee (Obstetrics and Gyneacology)
2002 -	Chairperson Priorities in Perinatal Care Association
2005 -	Member the PhD Committee of the Faculty of Health Sciences, University of Pretoria
2008 - 2011	Chairperson of the WHO AMSTL trial Data Management Committee
2009 -	Member of WHO Global Survey Steering Committee
2009	Chairperson of the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) – Facility Based Strategies & Constraints
2008 -	Member of National Perinatal Morbidity and Mortality Committee (NaPeMMCo)
2008 - 2010	Brazilian Network for Surveillance of Severe Maternal Morbidity
2009 -	Member of Maldives Steering Committee of Maternal and Perinatal Morbidity and Mortality Audit System
2009	Technical advisor – Zimbabwean Confidential Enquiry into Maternal Deaths
2009 -	Member of the Programme Advisory Committee, DFID funded Zimbabwe Maternal and Newborn Health Programme
2006	Technical Advisor, WHO on Monitoring and Evaluation for Maternal and Newborn Health and Services at District Level
2007 - 2010	Member of WHO Working Group on Maternal Mortality and Morbidity classifications
2010 -	Member of WHO Working Group on Perinatal Mortality and Morbidity classifications
2010	Member of Royal College Study Group on accelerating progress for reaching Millennium Goals 4 & 5
2009 -	Member of the Essential Steps in Managing Obstetric Emergency (ESMOE) Board, South Africa
2009 -	Lancet Working Group – Stillbirth series

Honors

1987 – 1988 South African Medical Research Council Post Graduate Bursary
1999 – 2002 Scientific Merit Award, University of Pretoria
2000 Certificate for Innovation in Education, University of Pretoria
2015 GSK Save the Children 2015 Health Care Innovation Award
2016 Havenga Medal from Suid Afrikaanse Wetenskap en Kuns for contribution to Health
2017 Exceptional Academic Achievement award, University of Pretoria
2017 Discovery Foundation Excellence award

C. Contributions to Science

1. Developing an international classification system for perinatal and maternal deaths: Part of the frustration of working in maternal and perinatal audit systems has been the multiple classification systems used to classify deaths. This has meant communication between countries and scientists was often confused. I was a member of the WHO ICD Maternal Mortality and the WHO ICD Perinatal Mortality working groups that developed standardized classification systems for maternal and perinatal deaths.

a. Allanson ER, Tunçalp Ö, Gardosi J, **Pattinson RC**, Francis A, Vogel JP, Erwich JJHM, Flenady VJ, Frøen JF, Neilson J, Quach A, Chou D, Mathai M, Say L, Gülmezoglu AM. The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM: results from pilot database testing in South Africa and United Kingdom. BJOG 2016 Nov;123(12):2019-2028 doi: 10.1111/1471-0528.14244. PMID: 27527122

b. Say L, Souza JP, **Pattinson RC**. Maternal near miss towards a standard tool for monitoring quality of maternal health care. Best Pract Res Clin Obstet Gynaecol. 2009 Jun; 23(3): 287-296. doi: 10.1016/j.bpobgyn.2009.01.007. PMID: 19303368.

2. Identifying problems and developing solutions: Improving maternal and perinatal care can only be performed in one has clearly identified the problems. I have developed audit systems for South Africa and used the audit results to develop interventions and assess their impact. This has helped to develop implementation science.

a. Allanson ER and **Pattinson RC**. Quality-of-care audits and perinatal mortality in South Africa. Bull World Health Organ. 2015 Jun;93(6), pp.424-8. doi: 10.2471/BLT.14.144683. PMID: 26240464 PMCID: PMC4450707.

b. Allanson ER, Muller M, and **Pattinson RC**. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. BMC Pregnancy and Childbirth. 2015 Feb 15;15:37. doi: 10.1186/s12884-015-0472-9. PMID: 25880128 PMCID: PMC4339432.

c. **Pattinson RC**, Makin JD, Say L, Bastos M. Critical incident audit and feedback to improve perinatal and maternal mortality and morbidity. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD002961 (update published in first edition 2011). PMID: 16235307 PMCID: PMC4171456.

d. De Knijf A, **Pattinson RC**. Confidential enquiries into quality of care of women in labour using Hypoxic Ischemic Encephalopathy as a marker. Facts Views Vis Obgyn. 2010;2(4):219-25. PMID: 25009710 PMCID: PMC4086007

3. Reducing stillbirths: Stillbirths are increasingly being recognized as an un-researched and under-appreciated area. I have been involved with research to bring this to the fore.

a. Frøen JF, Friberg IK, Lawn JE, Bhutta ZA, **Pattinson RC**, Allanson ER, Flenady V, McClure EM, Franco L, Goldenberg RL and Kinney MV. Stillbirths: progress and unfinished business. Lancet. 2016 Feb 6;387(10018):574-86. doi: 10.1016/S0140-6736(15)00818-1. PMID: 26794077.

b. Graham W, Wood S, Byass P, Filippi V, Gon G, Virgo S, Chou D, Hounton S, Lozano R, **Pattinson R** and Singh S. Diversity and divergence: the dynamic burden of poor maternal health. Lancet. 2016 Oct 29;388(10056):2164-2175. doi: 10.1016/S0140-6736(16)31533-1. PMID: 27642022.

c. Lawn JE, Blencowe H, **Pattinson R**, Cousens S, Kumar R, Ibiebele I, Gardosi J, Day L, Stanton C, for the Lancet Stillbirth Series steering team. Stillbirth - Where? When? Why? How to make the data count? Lancet. 2011 Apr 23;377(9775):1448-63. doi: 10.1016/S0140-6736(10)62187-3. PMID: 21496911

d. **Pattinson R**, Kerber K, Buchmann E, Friberg IK, Belizan M, Lansky S, Weissman E, Mathai M, Rudan I, Walker N, Lawn JE, for The Lancet's Stillbirths Series steering team. Stillbirths: how can health systems deliver for mothers and babies? Lancet. 2011 May 7;377(9777):1610-23. doi: 10.1016/S0140-6736(10)62306-9. PMID: 21496910.

4. Implementing strategies to reduce deaths: Identifying the problem is not enough and research into methods of implementation are critical. I have been involved with investigating this for some time.

a. Bergh, AM, Allanson E and **Pattinson RC**. 2015. What is needed for taking emergency obstetric and neonatal programmes to scale? Best Pract Res Clin Obstet Gynaecol. 2015 Nov;29(8):1017-27. doi: 10.1016/j.bpobgyn.2015.03.015. PMID: 25921973.

b. Bergh AM, Baloyi S and **Pattinson RC**. What is the impact of multi-professional emergency obstetric and neonatal care training? Best Pract Res Clin Obstet Gynaecol. 2015 Nov;29(8):1028-43. doi: 10.1016/j.bpobgyn.2015.03.017. PMID: 25937554.

c. Bergh A-M, Van Rooyen E, **Pattinson RC**. (2008). 'On-site' versus 'off-site' facilitation: a randomised trial of outreach strategies for scaling up kangaroo mother care. Human Resources for Health. 2008 Jul 23;6:13. No PMID.

d. Odendaal HJ**, Pattinson RC**, Bam R, Kotze TJ. Aggressive versus expectant management in women with severe preeclampsia between 28 and 34 weeks gestation: A randomized clinical trial. Obstet Gynecol 1990;76:1070-1075. No PMID.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

None

Recently Completed Research Support

Department for International Development (DFID) 1/1/2012 – 12/31/2016
Title: Scale-up Essential Steps in Managing Obstetric Emergencies
Role: PI

Centers for Disease Control U2GPS001053 1/1/2006 – 12/31/2014
Title: Use of Child Healthcare Problem Identification Program and Perinatal Problem Identification
Role: PI
Goal: Hospital-based child health care surveys using the Child Healthcare Problem Identification Programme (Child PIP) and the Perinatal Problem Identification Programme (PPIP) to monitor the impact of the prevention of mother to child transmission (PMTCT) of HIV and improve the quality of care of PMTCT delivery as well as overall quality of care

DFID 1/1/2012-12/31/2016
Title: Scale-up ESMOE and EOST
Role PI

European Union 1/1/2015 – 12/31/2018
Title: Scale-up Essential Steps in Managing Obstetric Emergencies
Role: PI

SAMRC/CSIR SHIP 1/1/2015 – 12/31/2018
Title: The role of continuous wave ultrasound of the umbilical artery in predicting and preventing stillbirths
Role: 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 FIVE PAGES.**

NAME: Koleka P Mlisana

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Executive Manager Academic Affairs, Research & Quality Assurance

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Natal	MB ChB	12/1986	Medicine
University of Natal	MMed Path(Microbiology)	12/1993	Medical Microbiology
University of KwaZulu Natal	PhD	12/2014	Medical Microbiology

A: Personal Statement

I am a Medical Microbiologist and currently the Executive Manager: Academic Affairs, Research & Quality Assurance at the NHLS in Sandringham; Johannesburg. Until recently I was the Head of Department of Medical Microbiology at the University of KwaZulu Natal and the National Health Laboratory Service in Durban, South Africa. I have worked in HIV research at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) for over 10 years focusing on HIV-1 subtype C pathogenesis and prevention in young women as well as doing HIV vaccine trials in KwaZulu Natal. My work included looking at the impact of sexually transmitted infections (STIs) and genital tract inflammation on HIV-1 acquisition and rate of disease progression in subtype C infected women wherein we showed similar levels of inflammation in both symptomatic and asymptomatic STIs resulting in increased risk of HIV acquisition.

In the past 5 years, my research focus has broadened to general microbiology, specifically TB diagnostics and drug resistance as well as establishing a molecular diagnostic platform for STIs. I am the UKZN representative and investigator on the DST-NRF Centre of Excellence in HIV Prevention grant in South Africa providing STI laboratory diagnosis and research for the programme. I also am the principal investigator for an NHLS Trust funded grant exploring rapid diagnostic methods in TB meningitis. Our group is also working on laboratory detection of rifampicin low level resistance in MTB using both phenotypic and genotypic techniques. We recently collaborated with an Emory University TB research group in an NIH funded study determining clinical outcomes in patients concurrently treated for MDR TB and HIV and a co-investigator in the study examining the transmission dynamics of XDR TB.

For this project, I will provide expert support for the implementation and operations of the GeneXpert diagnostic platform in all study clinics, ensure access to and abstraction of additional ANC and HIV-related laboratory test results from NHLS's laboratory information system, and facilitate data collection.

a. Shah NS, Auld SC, Brust JCM, Mathema B, Ismail N, Moodley P, **Mlisana K,** Allana S, Campbell A, Mthiyane T, Morris N, Mpangase P, van der Meulen H, Omar SV, Brown TS, Narechania A, Shaskina E, Kapwata T, Kreiswirth B, Gandhi NR. Transmission of Extensively Drug-resistant Tuberculosis in South Africa. N Engl J Med. 2017 Jan 19;376(3):243-253. doi: 10.1056/NEJMoa1604544. PMCID: PMC5330208.

b. Desjardins CA, Cohen KA, Munsamy V, Abeel T, Maharaj K, Walker BJ, Shea TP, Almeida DV, Manson AL, Salazar A, Padayatchi N, O'Donnell MR, **Mlisana KP,** Wortman J, Birren BW, Grosset J, Earl AM, Pym AS. Genomic and functional analyses of Mycobacterium tuberculosis strains implicate ald in D-cycloserine resistance. Nat Genet. 2016 May;48(5):544-51. PMCID: PMC4848111.

c. Cohen KA, Abeel, T, McGuire AM, Desjardins CA, Munsamy V, Shea TP, Walker BJ, Bantubani N, Almeida DV, Alvarado L, Chapman SB, Mvelase NR, Duffy EY, Fitzgerald MG, Govender P, Gujja S, Hamilton S, Howarth C, Larimer JD, Maharaj K, Pearson MD, Priest ME, Zeng Q, Padayatchi N, Grosset J, Young SK, Wortman J, **Mlisana KP,** O'Donnell MR, Birren BW, Bishai WR, Pym AS and Earl AM. Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of Mycobacterium tuberculosis Isolates from KwaZulu-Natal. PLoS Med. 2015 Sep 29;12(9):e1001880. PLoS Med 12, no. 9 (2015): e1001880. PMCID: PMC4587932.

d. Niehaus AJ, **Mlisana, K**, Gandhi NR, Mathema B, and Brust JCM. High Prevalence of inh A Promoter Mutations among Patients with Drug-Resistant Tuberculosis in KwaZulu-Natal, South Africa. PLoS One. 2015 Sep 2;10(9):e0135003. doi: 10.1371/journal.pone.0135003. PMCID: PMC4557915.

B. Positions and Honors

Positions & Employment:

1987	Intern, King Edward VIII Hospital, Durban, SA
1988	Medical Officer, Paediatrics Department at King Edward Hospital
1898 - 1993	Registrar in training, Department of Medical Microbiology, KEH VIII
1994 - 1995	Specialist Lecturer, Univ of Natal Medical School, Dept of Microbiology, Durban
1995 - 2002	Private pathology practice as a Microbiologist at Drs N.L. Pillay, Mackintosh & Partners Laboratory, now Lancet Laboratories.
2003 – 2009	Project Director, Centre for the AIDS Programme of Research in South Africa (CAPRISA)
2006 – 2009	Site Principal Investigator for South African AAIDS Vaccine Initiativ (SAAVI)
2007	National representative Principal Investigator for HIV Vaccine trial PAVE 100, HVTN
2007 – 2009	Head: CAPRISA HIV Vaccine Unit
2009 – 2011	Head: CAPRISA Pathogenesis and HIV Vaccine Programme
2011 – present	Head: Department of Medical Microbiology, NHLS & UKZN

Committee appointments:

2003	Scientific Committee - Coordinator for the HIV track: International Chemotherapy Congress
2007 – 2008	Member of the HVTN Efficacy Trials Design Working Group (ETDWG)
2007	Co-Chair of Basic and Clinical Sciences Track for SA AIDS 2007 Conference
2008	Co-Chair of the international AIDS Vaccine 2008 Conference
2008 – 2010	Member of the SA Medical Research Council Board Committee
2011 – 2015	Member of National Advisory Group on Immunisation Committee
2012 – 2014	Member of National Health Laboratory Service (NHLS) Board
2013	Conference Chair of the 6th SA AIDS 2013 Conference
2015 – present	Member of the Board of Trustees for South African National AIDS Council (SANAC)
2016	Co-chair of the Scientific Programme Committee for AIDS 2016 Conference
2016 – 2018	Member of the Ministerial Advisory Committee on Antimicrobial Resistance
Current	Protocol co-Chair of HVTN086/SAAVI103 Trial

Professional Memberships:

Health Professions Council of South Africa
South African Medical Association
Southern African HIV/AIDS Clinician's Society
Infectious Disease Society of South Africa
South African Society for Clinical Microbiologists

Honors:

2006 – 2007	Member of the Women's Global Health Scholars' Program, Fogarty International Center and Office of Women's Health, National Institutes of Health
2008 – 2009	International Advisory Board member of the University of Rochester Centre for AIDS Research (CFAR)

C. Contributions to Science

1. Drug resistant TB in South Africa: Some of our preliminary work has been to define the prevalence of both rifampicin and isoniazid resistance in the KZN province which is known to have the highest prevalence of MDR-TB in SA. With the recent roll-out of GeneXpert for diagnosis of TB in the country, it is critical to establish the prevalence of Rif monoresistance as Rif resistance is used as a surrogate for MDR-TB.

    a. Allana S, Shashkina E, Mathema B, Bablishvili N, Tukvadze N, Shah NS, Kempker RR, Blumberg HM, Moodley P**, Mlisana K**, Brust JC. pncA Gene Mutations Associated with Pyrazinamide Resistance in Drug-Resistant Tuberculosis, South Africa and Georgia. Emerging Infectious Diseases. Emerg Infect Dis. 2017 Mar;23(3):491-495. doi: 10.3201/eid2303.161034. PMCID: PMC5382742.

    b. O'Donnell MR, Pillay M, Pillay M, Werner L, Master I, Wolf A, Mathema B, Coovadia Y, **Mlisana K,** Horsburgh R, and Padayatchi N. Primary capreomycin resistance is common, and associated with early mortality in extensively drug-resistant tuberculosis (XDR-TB) patients in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2015 Aug 15;69(5):536-43. doi: 10.1097/QAI.0000000000000650. PMCID: PMC4501864.

    c. Dlamini-Mvelase NR, Werner L, Phili R, Cele LP, and **Mlisana, KP.** Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. BMC Infect Dis. 2014 Aug 16;14:442. doi: 10.1186/1471-2334-14-442. PMCID: PMC4141089.

    d. Coovadia YM, Mahomed S, Pillay M, Werner L, and **Mlisana, K.** Rifampicin mono-resistance in Mycobacterium tuberculosis in KwaZulu-Natal, South Africa: a significant phenomenon in a high prevalence TB-HIV region. PLoS One. 2013 Nov 6;8(11):e77712. doi: 10.1371/journal.pone.0077712. PMCID: PMC3819362.

2. The role of transmission in the spread of Drug-Resistant TB and the evolution of MDR-TB in South Africa: The development of drug resistant TB has always been thought to be as a result of poor or non-adherence to anti-TB treatment in patients with susceptible TB. The increase in patients diagnosed with MDR-TB without a previous history of TB challenged this dogma. As a result, we participated in a study that attempted to determine and quantify the role of transmission of MDR-TB in patients with no prior exposure to TB in the province of KwaZulu Natal in South Africa. Using whole genome sequencing, in collaboration with other researchers, we defined the evolution of XDR-TB over four decades showing isoniazid resistance as overwhelmingly the initial resistance mutation to be acquired.

    a. Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, **Mlisana K**, Allana S, Campbell A, Mthiyane T, Morris N. Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. N Engl J Med. 2017 Jan 19;376(3):243-253. doi: 10.1056/NEJMoa1604544. PMCID: PMC5330208.

    b. Cohen KA, Abeel T, McGuire AM, Desjardins CA, Munsamy V, Shea TP, Walker BJ, Bantubani N, Almeida DV, Alvarado L, Chapman SB, Mvelase NR, Duffy EY, Fitzgerald MG, Govender P, Gujja S, Hamilton S, Howarth C, Larimer JD, Maharaj K, Pearson MD, Priest ME, Zeng Q, Padayatchi N, Grosset J, Young SK, Wortman J, **Mlisana KP**, O'Donnell MR, Birren BW, Bishai WR, Pym AS and Earl AM. Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of Mycobacterium tuberculosis Isolates from KwaZulu-Natal. PLoS Med. 2015 Sep 29;12(9):e1001880. doi: 10.1371/journal.pmed.1001880. PMCID: PMC4587932.

    c. Lim JR, Gandhi NR, Mthiyane T, **Mlisana K**, Moodley J, Jaglal P, Ramdin N, Brust JC, Ismail N, Rustomjee R, Shah NS. Incidence and Geographic Distribution of Extensively Drug-Resistant Tuberculosis in KwaZulu-Natal Province, South Africa. PLoS One. 2015 Jul 6;10(7):e0132076. doi: 10.1371/journal.pone.0132076. PMCID: PMC4493033.

3. Impact of STIs and Genital inflammation on HIV-1 acquisition and rate of disease progression: Management of STIs for most inadequately resourced countries continues to be syndromic despite the high prevalence asymptomatic infections. We assessed the adequacy of syndromic diagnosis of STIs and evaluated the association between STI diagnosis and the risk of HIV acquisition in high risk women

in SA. Establishing an acute HIV infected cohort also allowed us to investigate rates of HIV disease progression in this community.

a. Masson L, Salkinder AL, Olivier AJ, McKinnon LR, Gamieldien H, **Mlisana K**, Scriba TJ, Lewis DA, Little F, Jaspan HB, Ronacher K. Relationship between female genital tract infections, mucosal interleukin-17 production and local T helper type 17 cells. Immunology. 2015 Dec;146(4):557-67. doi: 10.1111/imm.12527. PMCID: PMC4693890.

b. **Mlisana K,** Werner L, Garrett NJ, McKinnon LR, van Loggerenberg F, Passmore JS, Gray CM, Morris L, Williamson C, and Abdool Karim SS. Rapid disease progression in HIV-1 subtype C infected South African women. Clin Infect Dis. 2014 Nov 1;59(9):1322-31. doi: 10.1093/cid/ciu573. PMCID: PMC4271037.

c. **Mlisana K,** Sobieszczyk M, Werner L, Feinstein A, van Loggerenberg F, Naicker N, Williamson C, and Garrett N. Challenges of Diagnosing Acute HIV-1 Subtype C Infection in African Women: Performance of a Clinical Algorithm and the Need for Point-of-Care Nucleic-Acid Based Testing. PLoS One. 2013 Apr 30;8(4):e62928. doi: 10.1371/journal.pone.0062928. PMCID: PMC3639937.

d. **Mlisana K**, Naicker N, Werner L, Roberts L, van Loggerenberg F, Baxter C, Passmore JS, Grobler AC, Sturm AW, Williamson C, Ronacher K, Walzl G, Abdool Karim SS. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections and genital tract inflammation in high-risk women in South Africa**.** J Infect Dis. 2012 Jul 1;206(1):6-14. doi: 10.1093/infdis/jis298. PMCID: PMC3490689.

Complete list of published work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/koleka.mlisana.1/bibliography/45099467/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Active Research Support:

National Institutes of Health
1R01AI38646-01 **PIs: Gandhi and Mlisana** 04/01/2018 – 03/31/2023
Title: The role of casual contact and migration in XDR TB transmission in South Africa
Goal: To characterize and quantify the role of casual contact and migration in the transmission of XDR TB in South Africa, using genomic, geospatial and social network analysis.
Role: **Principal Investigator**

DST-NRF Centre of Excellence in HIV Prevention
UID 96354 **PI: Salim Abdool Karim** 03/01/2015 – 02/28/2020
University of KwaZulu Natal: Subcontract co-investigator
Title: Laboratory diagnosis and susceptibility testing of sexually transmitted pathogens.
Role: **UKZN Investigator**

DST-NRF SARChI **PI: Sabiha Essack** 02/01/2016 – 01/31/2020
Title: South African Research Chair in Antibiotic Resistance and One Health
Role: **Co-Investigator**

NHLS Research Trust
National Health Laboratory Service: **PI: Koleka Mlisana** 03/01/2016 – 02/28/2019
Title: Rapid Diagnosis of Tuberculous Meningitis: Detection of Tuberculostearic acid in Cerebrospinal Fluid.
Goal: To determine various diagnostic techniques (phenotypic and genotypic) for TBM as well as to develop and optimize a method for the detection of tuberculostearic acid for diagnosing TB meningitis.
Role: **Principal Investigator**

WHO **PI: Sabiha Essack** 01/31/2017 – 12/01/2019
Title: WHO Advisory Group on Integrated Surveillance of AMR (WHO-AGISAR) Grant
Goal: Triangulation of Antibiotic Resistance from Humans, the Food Chain and Associated Environments – A One Health Project
Role: **Co-Investigator**

Completed Research Support:

1R01AI089349 – 01 **PI: Gandhi** 4/1/2010 – 06/30/2016
NIH/NIAID R01 grant
Title: Transmission of HIV-associated XDR TB in Rural South Africa.
Goal: The goal of this study is to determine the proportion of XDR TB cases which arise from transmission and to identify locations and networks where transmission is occurring.
Role: **co- Investigator**

1R01AI087465 - 01A1 **PI: Gandhi** 07/01/2010 – 06/30/2016
NIH/NIAID R01 grant
Title: Impact of HIV, Antiretroviral Therapy and TB Genotype on Survival in MDR TB.
Goal: The goal of this study is to examine the impact of concurrent treatment of MDR TB and HIV on survival, treatment outcomes, adverse events and adherence in co-infected patients.
Role: **UKZN Principal Investigator**

Einstein Global Health Center pilot grant **PI: Brust** 03/01/2013–02/28/2015
Title: Prevalence of inhA Promoter Mutations in Patients with Drug-Resistant TB in KwaZulu-Natal, South Africa
Goal: The goal of this study is to determine the proportion of drug-resistant TB cases which are due to *inhA* promoter mutations in Kwa-Zulu Natal province, South Africa
Role: **UKZN co-Investigator**

A MRC – UK MRC Collaborative Research Programme On AMR PI: Essack 01/31/2017 – 12/31/2018
Title: eAMR: ICT Solutions for Real – Time Electronic Monitoring of AMU (use) and AMR in the one Health Approach
Role: **Co-Investigator**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Muzny, Christina A.

eRA COMMONS USER NAME (credential, e.g., agency login): CMUZNY

POSITION TITLE: Associate Professor of Medicine

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Texas at Austin; Austin, TX	BA	12/1998	Biology
Texas A&M College of Medicine; College Station, TX	MD	05/2003	Medicine
University of Mississippi Medical Center; Jackson, MS	Postdoctoral	06/2006	Internal Medicine
University of Mississippi Medical Center; Jackson, MS	Postdoctoral	06/2009	Infectious Diseases
University of Alabama at Birmingham School of Public Health; Birmingham, AL	MSPH	04/2017	Epidemiology; Clinical & Translational Science

A. Personal Statement

My clinical and research interests over the past 12 years have focused on sexually transmitted infections (STIs) (specifically vaginal infections including bacterial vaginosis (BV) and trichomoniasis) and HIV among difficult-to-reach populations of women, including women who have sex with women (WSW). My current NIAID K23-funded research focuses on investigating the pathogenesis of incident BV among WSW (a, b, c). I have also recently served as the UAB Site Principal Investigator on an NIAID R01-funded clinical trial with Dr. Kissinger to compare different dosing regimens of metronidazole for vaginal trichomoniasis among HIV-negative women (d). I am a teaching faculty for the AL-NC STD/HIV Prevention Training Center, an Associate Scientist for the UAB Center for AIDS Research, and a research mentor to two medical students, a junior faculty member in infectious diseases, and a biology master's graduate student. My infrastructure at UAB includes an experienced team of 2 research nurses, a laboratory technologist, a study coordinator, and two bioinformatics experts. I regularly collaborate with Drs. Taylor and Redden on vaginal microbiome research in addition to other experts. For the purposes of this R01, I will provide vaginal microbiome expertise related to study activities described in Aim 3.

1. **Muzny CA,** Blanchard E, Taylor C, et al. Identification of Key Bacteria Involved in the Induction of Incident Bacterial Vaginosis: A Prospective Study. J Infect Dis 2018; 218(6):966-978. PMID: 29718358. PMCID: PMC6093354.
2. **Muzny CA**, Lensing S, Aaron K, Schwebke JR. Incubation Period and Risk Factors Support Sexual Transmission of Bacterial Vaginosis in Women Who Have Sex with Women. Oral Presentation (Abstract #147) in Symposium 4, International Union for Sexually Transmitted Infections World Congress, Dublin, Ireland, June 28, 2018.
3. **Muzny CA,** Schwebke JR. Biofilms: An Underappreciated Mechanism of Treatment Failure and Recurrence in Vaginal Infections. Clin Infect Dis 2015;61(4):601-6. PMID: 25935553. Not NIH funded.
4. Kissinger P, **Muzny CA**, Mena L, et al. A randomized trial of metronidazole in a single 2 g dose versus 500 mg twice daily for 7 days for the treatment of trichomoniasis. Lancet Infect Dis 2018; 18(11):1251-1259. PMID: 30297322. PMCID: 6279510.

B. Positions and Honors

Positions and Employment

2005-2009	Medical Service, G.V. (Sonny) Montgomery Veterans Affairs Medical Center; Jackson, MS
2009-2010	Assistant Professor of Medicine, Infectious Diseases, Univ. of Mississippi Medical Center
2010-Present	Assistant Professor of Medicine, Infectious Diseases, Univ. of Alabama at Birmingham
2013-Present	Associate Scientist, Center for AIDS Research, Univ. of Alabama at Birmingham
2017-Present	Associate Professor of Medicine, Infectious Diseases, Univ. of Alabama at Birmingham

2018-2019 Medical Consultant for 2020 CDC STD Treatment Guidelines, Division of STD Prevention, Centers for Disease Control, Atlanta, GA
2019 Associate Professor of Epidemiology, Department of Epidemiology, Univ. of Alabama at Birmingham School of Public Health

Honors and Awards

1995-1998 Univ. of Texas at Austin College of Natural Sciences Dean's List
1997-1998 Univ. of Texas at Austin College Scholar
1999-2003 Honors Graduate, Texas A&M College of Medicine
2012-2013 Univ. of Alabama at Birmingham Department of Medicine Research Supplement Award
2012 Univ. of Alabama at Birmingham Department of Medicine Clinician Educator Award
2012 Travel Scholarship; 39th Annual Meeting of the Infectious Diseases Society of Gynecology
2014 Young Investigator Award; American Sexually Transmitted Diseases Association
2015-2016 Univ. of Alabama at Birmingham Department of Medicine Research Supplement Award
2017 Inspirational Physician Honoree; American Medical Association Women Physician's Section

Other Experience and Professional Memberships

2004-2018 Member, American College of Physicians
2006-Present Member, Infectious Diseases Society of America
2007-Present Member, American Society of Microbiology
2007-Present Member, American Sexually Transmitted Diseases Association
2007-2009 Graduate Medical Education Committee, Sub-Specialty Representative, Univ. of Mississippi
2014-Present Member, Institutional Review Board 02, Univ. of Alabama at Birmingham
2014-Present Contributing Member, f1000, Sexually Transmitted Diseases (without HIV) Section
2015 Ad Hoc Reviewer, NIAID R34 Clinical Trial Planning Grant Study Section
2015-Present Department of Medicine Peer Mentorship Committee, Univ. of Alabama at Birmingham
2015-Present Department of Medicine Research Development Group, Univ. of Alabama at Birmingham
2015-Present Member, Southern Society for Clinical Investigation
2016-Present Department of Medicine Scientific Review Committee, Univ. of Alabama at Birmingham
2016-Present Member, Infectious Diseases Society of Gynecology
2018-Present Fellow, American College of Physicians

C. Contributions to Science

1. **Research on the Pathogenesis of Bacterial Vaginosis**. My current research focuses on the pathogenesis of incident BV, the most common vaginal infection (a-d). With my K23 NIAID-funded mentored career development award, I am investigating the sequence of microbiological events prior to incident BV (#1 in Section A). A better understanding of the pathogenesis of incident BV is essential for improvements in BV diagnosis, treatment, and prevention.

    a. **Muzny CA**, Schwebke JR. Gardnerella vaginalis: Still a Prime Suspect in the Pathogenesis of Bacterial Vaginosis. Curr Infect Dis Rep 2013;15:130-5. PMID: 23371405. Not NIH funded.
    b. Schwebke JR, **Muzny CA,** Josey W. Role of Gardnerella vaginalis in the Pathogenesis of Bacterial Vaginosis – A Conceptual Model. J Infect Dis 2014;210(3):338-343. PMID: 24511102. Not NIH funded.
    c. **Muzny CA,** Schwebke JR. Accuracy of Self-Report of Sexual Activity among Adolescent Girls: Implications for Vaginal Flora Interpretations. mBio 2015; 6(3):e00819. PMCID: PMC4479702.
    d. **Muzny CA,** Schwebke JR. Pathogenesis of Incident Bacterial Vaginosis–Review of Current Hypotheses. J Infect Dis 2016;214 (S1):S1-5. PMID: 27449868. Not NIH funded.

2. **Research on the Microbiology, Epidemiology, and Treatment of Trichomoniasis in Women.** I have performed multiple studies regarding trichomoniasis from a microbiologic (a), epidemiologic (b, c), and treatment (d) perspective among women in high-risk clinical settings. My most recent work was on a multi-center NIAID-funded R01 clinical trial to compare different dosing regimens of metronidazole for treatment of trichomoniasis among HIV- women (d).

    a. **Muzny CA,** Rivers CA, Mena LA, et al. Genotypic Characterization of *Trichomonas vaginalis* Isolates among WSW in Sexual Partnerships. Sex Transm Dis 2012;39:556- 558. PMID: 22706219. Not NIH funded.

b. **Muzny CA,** Blackburn RJ, Sinsky RJ, et al. Added Benefit of Nucleic Acid Amplification Testing for the Diagnosis of *Trichomonas vaginalis* among Men and Women Attending a Sexually Transmitted Diseases Clinic. Clin Infect Dis 2014;59(6):834-841. PMID: 24928292. Not NIH funded.
c. **Muzny CA,** Burkholder GA, Fry KR, et al. Uptake of *Trichomonas vaginalis* Nucleic Acid Amplification Testing at an Urban HIV Clinic. Sex Transm Dis 2016;43(8):483-488. PMID: 27419815. Not NIH funded.
d. Kissinger P, **Muzny CA**, Mena L, et al. A randomized trial of metronidazole in a single 2 g dose versus 500 mg twice daily for 7 days for the treatment of trichomoniasis. Lancet Infect Dis 2018; 18(11):1251-1259. PMID: 30297322. PMCID: 6279510. (Duplicate from Section A).

3. **Research on the Sexual Health of African American Women Who Have Sex with Women (AAWSW) in the Southern United States**. I conducted the first studies of sexual risk behaviors and STI prevalence among AAWSW in the southern U.S. (a, b). Rates of trichomoniasis and chlamydia among this group of women were significantly higher than in previous studies of Caucasian WSW. I have also examined sexual and reproductive health indicators among Southern AAWSW by sexual identity and sexual behavior (c) and studied the association of psychosocial stressors with sexual behaviors, STI history, and STI diagnoses (d). Results helped tailor sexual health services provided to AAWSW.

    a. **Muzny CA,** Sunesara IR, Martin DH, et al. Sexually Transmitted Infections among African American Women Who Have Sex with Women: Does Sex with Men Make a Difference? Sex Transm Dis 2011;38:1118-1125. PMID: 22082722. Not NIH funded.
    b. **Muzny CA,** Austin EL, Harbison HS, et al. Sexual Partnership Characteristics of African American Women Who Have Sex with Women; Impact on Sexually Transmitted Infection Risk. Sex Transm Dis 2014;41:611-617. PMID: 25211257. Not NIH funded.
    c. Agénor M, Austin SB, Kort D, **Muzny CA**. Sexual Orientation and Sexual and Reproductive Health among Black WSW in the U.S. South. Women's Health Issues 2016;26(6):612-621. PMID: 27546567. Not NIH funded.
    d. **Muzny CA,** Pérez A, Eaton EF, et al. Psychosocial Stressors and Sexual Health among Southern African American Women Who Have Sex with Women. LGBT Health 2018; 5(4):234-241. PMID: 29688816. Not NIH funded.

4. **Cost-Effectiveness Research with an Emphasis on Sexually Transmitted Infections in People Living with HIV (PLWH).** I have found that, although the reverse syphilis-screening algorithm is more efficient than the traditional algorithm, it may lead to exorbitant costs for health systems serving PLWH (a). I have also found that compliance with STI screening practices among PLWH is costly (b). Sustainability will require critical analysis of true costs and cost effectiveness of STI screening tests.

    a. Eaton EF, Joe W, Kilgore ML, **Muzny CA**. Reverse syphilis screening algorithm fails to demonstrate cost effectiveness in persons living with HIV. Int J STD AIDS 2018;29(6):563-567. PMID: 29173098. PMCID: PMC6025800.
    b. Eaton EF, Hudak K, **Muzny CA**. Budgetary impact of compliance with STI screening guidelines in persons living with HIV. J Acquir Immune Defic Syndr 2017;74(3):303-308. PMID: 27787348. PMCID: PMC5303178.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Dq0c42rn4QN/bibliography/47636050/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

2018/04/01-2019/03/31
No number assigned, UAB STI Cooperative Research Center Developmental Award
Eaton, Ellen (PI)
Analyzing Syphilis Incidence and Risk in MSM at an Urban HIV PrEP Clinic
The primary goal of this award is to determine the incidence and predictors of infection with early syphilis among MSM receiving care in an urban PrEP clinic in the Deep South in order to inform a mathematical model on the comparative effectiveness of STI PEP.

Role: Co-Investigator/Research Mentor

2017/03/01-2019/02/28
No number assigned, UAB Center for AIDS Research Developmental Award
Eaton, Ellen (PI)
Identifying Patient-Centered Sexually Transmitted Infection Testing Services to Reduce HIV/STI Transmission in Young African American Men Who Have Sex with Men
The goal of this award is to develop a set of patient-centered STI testing option attributes for young African American MSM using qualitative research to inform a quantitative study.
Role: Co-Investigator/Research Mentor

2015/07/01-2019/06/30
No number assigned, University of Alabama at Birmingham IMPACT Award
Muzny, Christina A. (PI)
Pathogenesis of Bacterial Vaginosis among Women Who Have Sex with Women
The goal of this award is to provide supplemental funds to conduct K23-related research activities.
Role: Principal Investigator

2014/07/01-2019/06/30
U19AI113212, NIH/NIAID/DHHS
Hook, Edward (PI)
UAB Sexually Transmitted Infections Cooperative Research Center Project 2: Strain Diversity among Gardnerella: Association with Progression to BV (Schwebke, PI)
The goal of this award is to characterize virulence factors of *Gardnerella vaginalis* isolates obtained in close proximity to incident BV. The virulence factors of these isolates will be compared to those of control strains isolated from the same woman several weeks prior to incident BV and from women who did not progress to BV.
Role: Co-Investigator

2014/06/01-2019/05/31
K23AI106957, NIH/NIAID
Muzny, Christina A. (PI)
Pathogenesis of Bacterial Vaginosis among Women Who Have Sex with Women
The goal of this award is to use molecular methods to determine the sequence of microbiological events culminating in incident BV among sexually active African American WSW.
Role: Principal Investigator

Completed Research Support (Past 3 Years)

R01AI097080 Supplement Kissinger, Patricia (PI) 06/30/16 – 06/30/18
NIH/NIAID
Trichomonas vaginalis DNA Clearance and Specimen Repository Study

R01AI097080 Kissinger, Patricia (PI) 08/15/13 – 06/30/18
NIH/NIAID
Trichomonas vaginalis Repeat Infections among HIV-Negative Women

UL1TR001417 Muzny, Christina (PI) 04/04/16 – 03/31/17
NIH/NCATS, CCTS Multidisciplinary Network Pilot Program Award
Genital Microbiomes of Women with Recurrent BV and their Regular Male Sexual Partners

HHSN272201100034C, NIH/NIAID 09/28/11 – 08/15/18
Kimberlin, David (PI)
Identification of Herpes Simplex Virus (HSV) Shedding in the Female Genital Tract of Pregnant and Non-Pregnant Women by the Xpert HSV ½ Assay, Routine PCR, and Culture
The goals of this award are to estimate the sensitivity of the Xpert HSV 1/2 Assay relative to culture for detecting HSV DNA in the genital tract of pregnant and non-pregnant women in STI clinics.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: David T. Redden

eRA COMMONS USER NAME (credential, e.g., agency login): DRedden

POSITION TITLE: Professor, Biostatistics

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama, Tuscaloosa, Alabama	PhD	06/1995	Applied Statistics
University of Alabama, Tuscaloosa, Alabama	MS	06/1993	Applied Statistics
Auburn University, Auburn, Alabama	BS	06/1991	Mathematics

A. Personal Statement

I have 24 years of experience as **a clinical trials biostatistician** and university professor. I have served as Principal Investigator of a K25 award that developed statistical methods to estimate and control for the effects of admixture within genetic association studies. As the former Principal Investigator of the NIAMS Multidisciplinary Clinical Research Center (MCRC) Methodology Core, I mentored junior investigators and oversaw the design, data collection and management, and analysis of the MCRC projects. These 4 projects included an outcome and effectiveness research study, two genetic association studies, and an imaging study. I have also served as Co-PI and Statistician on multiple R01 grants and longitudinal studies investigating AIDS, Diabetes, Obesity, Tuberculosis, Asthma, Early Childhood Education, Nutrition, Gerontology, Urinary Incontinence, and Pain. I currently serve on the Executive Committee of the UAB Center for Clinical and Translational Science (CCTS) and I am Senior Statistician of Biostatistics, Epidemiology, and Research Division of the CCTS. I have expertise in design and analysis of clustered trials, group randomized trials, non-inferiority designs, power calculations, generalized estimating equations, and regression methodology including hierarchical linear models, mixed linear models, repeated measures ANOVA, and clinical trial design. I have served as biostatistician, designing, overseeing data management, and conducting analyses for Phase I, II, and III clinical trials investigating STI, and HIV related malignancies. In my role as PI of MCRC methodology core, I have regularly collaborated with Drs. Muzny and Taylor on vaginal microbiome research (a,b). <u>For this study, I will serve as the lead biostatistician.</u>

a) Muzny CA, Blanchard E, Taylor C, et al. Identification of Key Bacteria Involved in the Induction of Incident Bacterial Vaginosis: A Prospective Study. J Infect Dis 2018 Aug 14, 218(6): 966-978. PMID: 29718358. PMCID: PMC6093354.

b) Van Der Pol WJ, Kumar R, Morrow CD, Blanchard EE, Taylor CM, Martin DH, Lefkowitz EJ, Muzny CA. In Silico and Experimental Evaluation of Primer Sets for Species Level Resolution of the Vaginal Microbiota using 16S rRNA Gene Sequencing. J Infect Dis 2019 Jan 7, 219(2): 305-314. PMID: 30535155. PMID in process.

B. Positions and Honors

<u>Positions and Employment</u>

1995 – 1996 Post-Doctoral Fellow, University of Alabama at Birmingham, Civitan International Research Center

1996 – 1999 University of Alabama at Birmingham, Research Assistant Professor, Division of Medical Statistics, Department of Hematology and Oncology, School of Medicine
1999 – 2001 Research Triangle Institute, Statistician, Statistical Research Division
2001 – 2004 University of Alabama at Birmingham, Assistant Professor, Department of Biostatistics, School of Public Health.
2002 – 2009 Veterans Administration Hospital, Birmingham AL, Research Statistician, Geriatric Research, Education and Clinical Center
2004 – 2012 University of Alabama at Birmingham, Associate Professor, Department of Biostatistics, School of Public Health
2012 – University of Alabama at Birmingham, Full Professor, Department of Biostatistics, School of Public Health
2014 – 2017 University of Alabama at Birmingham, Chair, Department of Biostatistics, School of Public Health
2017 - University of Alabama at Birmingham, Vice-Chair, Department of Biostatistics, School of Public Health

C. Contribution to Science

1. **Development of New Statistical Methodology.** Over the past 20 years, I have had the privilege to work on many challenging and innovative clinical research projects. Within several clinical research projects, hypotheses are often presented and data are collected that do not have appropriate statistical methods. From those studies, I have had the opportunity to work with graduate students, post-doctoral fellows, and other researchers on developing new statistical methods in group randomized trials, quantile regression, genetic association studies, and clinical trials. Below is subset of my published articles focusing on statistical methods.

   a) Cui X, Yu S, Tamhane A, Causey ZL, Steg A, Danila MI, Reynolds RJ, Wang J, Wanzeck KC, Tang Q, Ledbetter SS, **Redden DT**, Johnson MR, Bridges SL Jr. Simple regression for correcting ΔCt bias in RT-qPCR low-density array data normalization. *BMC Genomics* 2015; 16(1):1274. PubMed PMID: 25776666. PMCID: PMC4335788

   b) Li P, **Redden DT**. Small sample performance of bias-corrected sandwich estimators for cluster-randomized trials with binary outcomes. *Stat Med*. 2015; 34(2):281-96. PubMed PMID: 25345738; PubMed Central PMCID: PMC4268228.

   c) Richardson E, **Redden DT**. Moving towards multiple site outcomes in spinal cord injury pain clinical trials: An issue of clustered observations in trial design and analysis. *J Spinal Cord Med*. 2014; 37(3):278-87. PubMed PMID: 24621021; PubMed Central PMCID: PMC4064577.

   d) **Redden DT**, Fernández JR, Allison DB. A simple significance test for quantile regression. *Stat Med.* 2004; 23(16):2587-97. PubMed PMID: 15287086.

2. **Conduct and Analysis of Cluster Designs/Group Randomized Trials.** In 1995, the first NIH research project on which I worked was a multi-site study that followed the development of children over time. Within that project, I learned about cluster randomized trials and hierarchical linear models. Both of those topics have fascinated me over my career, and I have had the opportunity to reuse the skills developed during that period for clustered designs in tuberculosis, osteoporosis screening, AIDS research, and spinal cord injury research. Below is subset of my published articles focusing on cluster designs.

   a) Bailey FA, Williams BR, Woodby LL, Goode PS, **Redden DT**, Houston TK, Granstaff US, Johnson TM 2nd, Pennypacker LC, Haddock KS, Painter JM, Spencer JM, Hartney T, Burgio KL. Intervention to improve care at life's end in inpatient settings: the BEACON trial. *J Gen Intern Med*. 2014; 29(6):836-43. PMID: 24449032; PMCID: PMC4026508.

   b) Warriner AH, Outman RC, Feldstein AC, Roblin DW, Allison JJ, Curtis JR, **Redden DT**, Rix MM, Robinson BE, Rosales AG, Safford MM, Saag KG. Effect of self-referral on bone mineral density testing and osteoporosis treatment. *Med Care*. 2014; 52(8):743-50. PMID: 24984211; PMCID: PMC4101066.

   c) Megazzini KM, Sinkala M, Vermund SH, **Redden DT**, Krebs DW, Acosta EP, Mwanza J, Goldenberg RL, Chintu N, Bulterys M, Stringer JS. A cluster-randomized trial of enhanced labor ward-based

PMTCT services to increase nevirapine coverage in Lusaka, Zambia. *AIDS* 2010; 24(3):447-55. PMID: 19926959. No NIH Funding.

d) Bailey WC, Gerald LB, Kimerling ME**, Redden D**, Brook N, Bruce F, Tang S, Duncan S, Brooks CM, Dunlap NE. Predictive model to identify positive tuberculosis skin test results during contact investigations. *JAMA* 2002; 287(8):996-1002. PMID: 11866647.

3. Collaborative Research focusing on Pain Disparities. In 2005, I served as Principal Investigator of the Multidisciplinary Clinical Research Center (MCRC). Many of the projects focused on pain research and these projects lead to a collaborative study with the University of Florida examining the racial disparity in reported pain. This collaboration, which includes the PI of this proposed project, is ongoing.

a) Petrov ME, Goodin BR, Cruz-Almeida Y, King C, Glover TL, Bulls HW, Herbert M, Sibille KT, Bartley EJ, Fessler BJ, Sotolongo A, Staud R, **Redden D**, Fillingim RB, Bradley LA. Disrupted Sleep is Associated with Altered Pain Processing by Sex and Ethnicity in Knee Osteoarthritis. *J Pain*. 2015; 16(5):478-90. PMID: 25725172. PMCID: PMC4424160

b) Glover TL, Goodin BR, King CD, Sibille KT, Herbert MS, Sotolongo AS, Cruz-Almeida Y, Bartley EJ, Bulls HW, Horgas AL, **Redden DT**, Riley JL 3rd, Staud R, Fessler BJ, Bradley LA, Fillingim RB. A Cross-Sectional Examination of Vitamin D, Obesity, and Measures of Pain and Function in Middle-Aged and Older Adults with Knee Osteoarthritis. *Clin J Pain*. 2015 Jan 7. PMID: 25569220. PMCID: PMC4494986.

c) Goodin BR, Bulls HW, Herbert MS, Schmidt J, King CD, Glover TL, Sotolongo A, Sibille KT, Cruz-Almeida Y, Staud R, Fessler BJ, **Redden DT**, Bradley LA, Fillingim RB. Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and older with knee osteoarthritis: ethnic differences. *Psychosom Med*. 2014; 76(4):302-10. PMID: 24804882; PMCID: PMC4066647.

d) Goodin BR, Pham QT, Glover TL, Sotolongo A, King CD, Sibille KT, Herbert MS, Cruz-Almeida Y, Sanden SH, Staud R, **Redden DT**, Bradley LA, Fillingim RB. Perceived racial discrimination, but not mistrust of medical researchers predicts the heat pain tolerance of African Americans with symptomatic knee osteoarthritis. *Health Psychol*. 2013; 32(11):1117-26. PMID: 24219416; PMCID: PMC3943939.

4. Collaborative Research in Organ Donation and Transplant Research. Over the past 10 years, I have worked closely with investigators involved in organ donation and transplant research. I collaborated with Derek Dubay, MD, in the development of his Mentored Patient-Oriented Research Career Development Award (K23). This K award was instrumental in setting the stage for a recent R03 award. The collaboration has led to numerous collaborative papers of which a subset is listed below.

a) White JA, **Redden DT**, Bryant MK, Dorn D, Saddekni S, Abdel Aal AK, Zarzour J, Bolus D, Smith JK, Gray S, Eckhoff DE, DuBay DA. Predictors of repeat transarterial chemoembolization in the treatment of hepatocellular carcinoma. *HPB (Oxford)*. 2014; 16(12):1095-101. PMID: 25158123; PMCID: PMC4253333.

b) DuBay DA, Ivankova N, Herby I, Wynn TA, Kohler C, Berry B, Foushee H, Carson AP, **Redden DT**, Holt C, Siminoff L, Fouad M, Martin MY. African American organ donor registration: a mixed methods design using the theory of planned behavior. *Prog Transplant*. 2014; 24(3):273-83. PMID: 25193729; PMCID: PMC4377221.

c) DuBay DA, **Redden DT**, Bryant MK, Dorn DP, Fouad MN, Gray SH, White JA, Locke JE, Meeks CB, Taylor GC, Kilgore ML, Eckhoff DE. Resource utilization associated with procurement of transplantable organs from donors that do not meet OPTN eligible death criteria. *Transplantation* 2014; 97(10):1043-8. PMID: 24503760; PMCID: PMC4024080.

d) DuBay D, **Redden D**, Haque A, Gray S, Fouad M, Siminoff L, Holt C, Kohler C, Eckhoff D. Is decedent race an independent predictor of organ donor consent or merely a surrogate marker of socioeconomic status? *Transplantation* 2012; 94(8):873-8. Erratum in: Transplantation. 2013; 95(4):e23. PMID: 23018878; PMCID: PMC3566527.

5. **Collaborative Research in End of Life Care.** Over the past 15 years, I have served as the lead statistician for the Department of Veterans Affairs Birmingham/Atlanta Geriatric Research Education and Clinical Center (GRECC). Within this collaborative effort, I have designed numerous clinical trials, multiple pilot studies, a cluster design study for improving end of life care, and a new group randomized trial. This long standing collaboration has been very productive and a subset of the published papers is listed below.

   a) Johnson TM 2nd, Markland AD, Goode PS, Vaughan CP, Colli JL, Ouslander JG**, Redden DT**, McGwin G, Burgio KL. Efficacy of adding behavioural treatment or antimuscarinic drug therapy to α-blocker therapy in men with nocturia. *BJU Int*. 2013; 112(1):100-8. PMID: 23448285. No NIH Funding.

   b) Gleason JL, Richter HE, **Redden DT**, Goode PS, Burgio KL, Markland AD. Caffeine and urinary incontinence in US women. *Int Urogynecol J*. 2013; 24(2):295-302. PMID: 22699886; PMCID: PMC3505252.

   c) Bailey FA, Williams BR, Goode PS, Woodby LL, **Redden DT**, Johnson TM 2nd, Taylor JW, Burgio KL. Opioid pain medication orders and administration in the last days of life. *J Pain Symptom Manage*. 2012; 44(5):681-91. PMID: 22765968. No NIH Funding.

   d) Bailey FA, Allen RS, Williams BR, Goode PS, Granstaff S, **Redden DT**, Burgio KL. Do-not-resuscitate orders in the last days of life. *J Palliat Med*. 2012; 15(7):751-9. PMID: 22536938. No NIH Funding.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/david.redden.1/bibliography/47766083/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

P60 AR064172 (Redden) 09/16/2013 – 07/31/2019
Methodology Core for the Multidisciplinary Clinical Research Center (MCRC)
The core is responsible for the design and analysis of 4 novel research projects in rheumatoid arthritis and musculoskeletal diseases. The methodology core is also responsible for the methods development and publication. Role: PI

R37 AR033906 (Bradley) 09/15/2014 – 04/30/2019
Ethnic Differences in Responses to Painful Stimuli (UPLOAD)
The proposed study will be the first to directly investigate ethnic group differences in central pain processing and to prospectively characterize the temporal development and mediators of changes in central pain processing contributing to ethnic group differences in knee osteoarthritis-related pain. Role: Co-Investigator

P50 AR060772 (K. Saag) 09/01/2012 – 08/31/2019
Centers of Research Translation (CoRT)
CoRT will support the conduct of innovative translation research and the training of clinical investigators in gout and hyperuricemia. The overall goal of the UAB CoRT is to improve the health care of patients with gout and hyperuricemia by applying scientifically rigorous, state-of-the-art methodology to clinically important questions in translational investigation. Role: Co-Investigator

UL1 TR001417 (Kimberly) 08/18/2015 – 03/31/2019
UAB Center for Clinical and Translational Science (CCTS)
The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability. Role: BERD Co-Lead

VA IPA Agreement (Burgio) 09/01/2015 – 08/31/2019
Evaluation of Methods for Implementation of a Comfort Care Order Set - BEACON II
This is a cluster randomized trial of 48 Veteran Administration hospitals comparing the effectiveness of in-person hospice training versus remote learning practices using a randomization plan, data collection and analyses. Role: Investigator

0000-044-01-03 (Korf) 08/01/2017 – 5/31/2021
Clinical Sequencing Across Communities in the Deep South (CSER2)
A major goal of CSER2 is to try to empower non-genetics trained health professionals to explain the results of genomic testing to families. Because of a shortage of trained medical geneticists, we need new paradigms in order to provide the benefits of genomic testing to more patients. The need is especially acute in our underserved populations.

Recently Completed Research Support

P50 AR060772 (K. Saag) 09/01/2012 – 08/31/2018
Centers of Research Translation (CoRT)
CoRT will support the conduct of innovative translation research and the training of clinical investigators in gout and hyperuricemia. The overall goal of the UAB CoRT is to improve the health care of patients with gout and hyperuricemia by applying scientifically rigorous, state-of-the-art methodology to clinically important questions in translational investigation. Role: Co-Investigator

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1. Vertebrate Animals Section

Are vertebrate animals euthanized? ☐ Yes ☐ No

If "Yes" to euthanasia

Is method consistent with American Veterinary Medical Association (AVMA) guidelines? ☐ Yes ☐ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*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.

*Budget Period *Anticipated Amount ($) *Source(s)

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

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 Cover Page Supplement

4. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ☐ Yes ☐ No

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

*Previously reported: ☐ Yes ☐ No

5. Change of Investigator / Change of Institution Section

☐ Change of Project Director / Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

☐ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

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1. Introduction to Application (or Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	Specific_Aims_STI_R01_Feb_2019_rev1054114386.pdf
3. Research Strategy*	Research_Strategy_STI_R011054114124.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	Multi_PI_Plan1054050481.pdf
8. Consortium/Contractual Arrangements	Consortium_Agreement__2_1054114161.pdf
9. Letters of Support	STI_R01_LOS1054114151.pdf
10. Resource Sharing Plan(s)	Resource_sharing_plan1054050482.pdf
11. Authentication of Key Biological and/or Chemical Resources	Authentication_of_Key_Resources1054050478.pdf
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SPECIFIC AIMS

Sexually transmitted infections (STIs) during pregnancy cause adverse birth outcomes such as preterm birth, low birth weight, perinatal death, and congenital infections including increased mother-to-child HIV transmission.[1-12] Though STIs are common in pregnant women globally, WHO's current syndromic management guidelines focusing on symptomatic infections continue to result in the majority of STIs (most of which are asymptomatic) remaining untreated during pregnancy.[13-18] To study the benefit, acceptability and feasibility of STI diagnostic screening, we integrated point-of-care molecular testing for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) into **antenatal care (ANC)** services (NICHD R21HD084274) for HIV-infected pregnant women in South Africa. We found diagnostic screening and immediate treatment during ANC to be highly acceptable and feasible;[19] 97.8% agreed to be tested and >93% received same-day treatment. Of 430 women screened, 41% had an STI (65% were asymptomatic).[19] Our intervention decreased prevalent STIs at delivery by >50% compared to women who received standard-of-care syndromic management.

Though acceptable, feasible and effective, our previous study had limitations. First, we detected a 9.1% cumulative incidence of STIs between first ANC and delivery, suggesting a single diagnostic screening with appropriate treatment at ANC enrollment may not optimally decrease STIs at time of delivery. Consequently, *evaluating the impact and cost effectiveness of different screening strategies to decrease STIs during pregnancy is urgently needed.* Second, our study was underpowered to detect an effect on birth outcomes. Demonstrating the impact of diagnostic screening and treatment, compared to syndromic management, on birth outcomes will provide critical evidence to update WHO's syndromic management guidelines during pregnancy. Third, we found a 26.5% STI positivity at test-of-cure. Though studies suggest that untreated partners are the primary cause of persistent STI positivity in women, in our study among women with a treated partner, persistent STIs were still high. Consequently, *biological factors that increase the risk for STI persistence must be further investigated.*

Research suggests the **vaginal microbiome** plays a critical role in STI acquisition, persistence, and treatment outcomes. Vaginal **community state types (CST)** with different concentrations of *Lactobacillus (L.)* species are associated with increased risk of acquiring STIs.[20-24] *In vitro* studies revealed certain vaginal bacteria can inactivate metronidazole,[25-27] standard TV treatment, and **bacterial vaginosis** (**BV**; CST-4) influenced TV treatment outcomes in HIV-infected women.[28] Vaginal microbiomes dominated by *L. crispatus*, *L. gasseri* and *L. vaginalis* may inhibit CT elementary bodies, while *L. iners may* increase the risk and duration of CT infection.[21,29,30]

To 1) identify optimal, cost-effective screening strategies that decrease the burden of STIs during pregnancy and reduce adverse birth outcomes, 2) provide evidence to update WHO's syndromic management guidelines, and 3) elucidate the role of the vaginal microbiome in STI treatment outcomes, we propose three Specific Aims:

Aim 1: Evaluate three different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes. Hypothesis 1 (H1): Compared to a one-time diagnostic test for STIs at a woman's first ANC visit, repeat testing algorithms will significantly reduce adverse birth outcomes. H2: Compared to diagnostic screening with follow-up test-of-cure (ToC), repeat screening and treatment without any ToC will significantly decrease STIs at delivery. Approach: A three-arm randomized controlled hybrid-effectiveness trial will be conducted; **Arm 1**) diagnostic screening and treatment at first ANC + ToC follow-up; **Arm 2**) repeat screening and treatment throughout ANC (no ToC); **Arm 3**) one-time diagnostic screening and treatment at first ANC, no ToC (control). Prevalence and incidence of CT, NG and TV at delivery and frequency of adverse birth outcomes by study arm will be assessed.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and disability-adjusted life-year (DALY) averted. H1: Compared to one-time diagnostic screening and treatment at first ANC, diagnostic screening with follow-up ToC and repeated screening with treatment (no ToC) will be more cost-effective to avert STIs at delivery, and reduce adverse birth outcomes. Approach: We will estimate and compare the costs of different STI screening strategies relative to control, and the costs of managing adverse birth outcomes. Decision analytic modeling will estimate the cost-effectiveness per STI and DALY averted.

Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women. H1: CT-infected pregnant women with BV-associated vaginal microbiota CSTs will be significantly more likely to have persistent infections at test-of-cure compared to women with non-BV associated CSTs. Approach: A nested case-control (1:2) study using vaginal specimens collected from CT-infected women at first ANC, 1, 2 and 3 weeks post-treatment.

We will enroll 2500 pregnant women (50% HIV-infected/ 50% HIV-uninfected) from ANC clinics in Tshwane District (ANC HIV positivity= 23.4%[31]), South Africa. Our research team has expertise and experience in all aspects of the proposed study including prior work at study sites. Multi-institutional collaborations allow us to leverage unique implementation platforms and resources, and allow for rapid dissemination of findings.

RESEARCH STRATEGY

SIGNIFICANCE

HIV and STIs among pregnant women in South Africa are a major problem. In 2013, the South African government estimated that 29.7% of women seeking antenatal care (ANC) were HIV-infected,[31] a prevalence that has remained relatively stable since 2007. That high HIV prevalence is compounded by high rates of STIs in women of reproductive age.[32-34] Our recent study using molecular testing found 40.5% of HIV-infected pregnant women at their first ANC visit were infected with CT, NG and/or TV; 65% were asymptomatic (Table 1).[19] Given that most STIs in women are asymptomatic and that the South African government currently only recommends symptomatic screening and syndromic management in line with WHO guidelines, the majority of STIs in HIV-infected South African pregnant women go undiagnosed and untreated.

STIs are associated with adverse birth outcomes and mother-to-child-transmission (MTCT) of HIV. Untreated CT, NG and TV infections during pregnancy are associated with intrauterine growth retardation, low birth weight (LBW), preterm delivery, and premature rapture of membranes.[35-45] Infants in South Africa routinely receive chloramphenicol eye ointment at birth to prevent neonatal bacterial conjunctivitis, most often caused by untreated maternal CT or NG infection.[46] Yet the risks to infants born to HIV-infected mothers are greater than conjunctivitis. A study of HIV-infected women in Tanzania found that NG co-infection increased intrauterine HIV transmission by >450%.[2] **Our team's prior work** in an NICHD HPTN 040 sub-study demonstrated that CT/NG infection increased HIV MTCT by 160% (RR=2.6, 1.1 – 5.8).[9] Prior research in non-pregnant women suggests that STIs in HIV-infected women may augment the risk of HIV transmission by increasing localized inflammatory responses and viral shedding;[47-56] treatment of those STIs reduced HIV transmission.[57,58] Our own study in HIV-infected pregnant women in South Africa documented 34.8% (of 731) with adverse birth outcomes including 17.8% with preterm delivery, 14.8% low birth weight and 4.8% stillbirth (see *Preliminary Studies* section).[19]

Table 1: Prevalence of *Chlamydia trachomatis (CT)*, *Neisseria gonorrhoeae (NG)* and *Trichomonas vaginalis (TV)* among HIV-infected pregnant women in three healthcare facilities in Tshwane District, South Africa (N=430)[19]

	N+	%	95% CI	% Asymptomatic
Any STI (CT/NG/TV)	174	40.5%	36.1% - 45.5%	64.9%
Any CT infection	127	29.6%	25.4% - 34.2%	62.6%
Any NG infection	24	5.6%	3.9% - 8.5%	50.0%
Any TV infection	86	20.0%	16.7% - 24.5%	53.6%

Current WHO STI screening recommendations, especially during pregnancy, leave a large burden of disease undetected and untreated. WHO recommends syndromic management of STIs in resource-limited settings due to its low cost and the unavailability of appropriate laboratory infrastructure.[59,60] Syndromic management involves treating STIs based on an algorithm of common symptoms. As our own research[19] (Table 1) and others have shown, most STIs are asymptomatic and go untreated in settings where syndromic management is used.[18,61,62] Major limitations of syndromic management include: 1) non-determination of infectious etiologies, 2) limited specificity, especially during pregnancy, of "symptoms" algorithms, and 3) inappropriate treatment or over-treatment.[62,63] Diagnosis of STIs has traditionally relied on culture and microscopy; even when highly sensitive PCR assays became available, dedicated lab infrastructure and trained laboratory personnel were required.[64-66] However, with the advent of new, rapid, easy-to-use PCR-based 'near-patient' or **'point-of-care' (PoC)** technology for the diagnosis of STIs,[67,68] our team has shown in multiple settings like Haiti, Vietnam, Botswana, Peru and South Africa that the implementation of diagnostic screening in variety of clinical settings is now possible.[19,69-73] Despite that, optimal models for PoC testing, especially during pregnancy, have not been identified. That is further highlighted by our recent work integrating PoC diagnostic screening for CT, NG and TV into ANC services for HIV-infected pregnant women in South Africa. Specifically, while single PoC screening, treatment and test-of-cure decreased the prevalence of STIs at time of delivery by >50% compared to syndromic management, incident infections were not identified or treated, leaving many women with STIs at time of delivery.

South African and international decision-makers require data on the cost and cost-effectiveness of STI screening and treatment programs. The South African *National Strategic Plan for HIV, TB and STIs 2017-2022*[74] includes recommendations for the detection and treatment of STIs, including through PoC testing. However, while some efforts are underway to plan for those interventions, to date, no South African study exists to inform those costing and budgeting efforts. Estimates from our proposed study can also inform policy decisions in other low-middle income countries, as well as WHO recommendations for the management of STIs during pregnancy. Ultimately, developing, evaluating and costing STI PoC testing algorithms, especially those implemented during antenatal care, is a very high global health priority (see letter of support from the WHO).

Risk factors associated with persistent STIs must be better understood. Given the increased risks of adverse outcomes from STIs during pregnancy, it is imperative that infections are cleared following treatment. This is especially important amongst HIV-infected pregnant women, where STIs may increase the risk of MTCT of HIV. As part of our recent study integrating molecular screening for CT, NG and TV into ANC services, we

performed test-of-cure until a participant cleared their infection, or had a documented birth outcome.[75,76] At the first test-of-cure, 26.5% were persistently positive; a number of women required multiple rounds of treatment before clearing their infection (Table 2). Interviews with women suggest that behaviors associated with poor treatment adherence or re-exposure from untreated partners cannot fully explain the high persistent positivity with CT or TV.[77] For those with a positive TV test following treatment, evidence is mounting that clinical treatment failure, rather than organism-specific metronidazole resistance or reinfection, is likely.[28,77-79] Gatski *et al.*[28] revealed that in HIV+/TV+ women, concomitant BV was significantly associated with metronidazole treatment failure, suggesting that the vaginal environment associated with BV decreased the efficacy of metronidazole. This hypothesis is supported by *in vitro* studies that have shown that metronidazole can be inactivated by certain bacteria present in the vaginal microbiome.[25-27] Repeat CT positivity following treatment is not well understood; CT antimicrobial resistance is exceedingly rare.[80] Reports have suggested that heterotypic resistance associated with high organism loads may factor in persistent infections; however, the evidence is limited.[80-83] Given that multiple rounds of repeated test-of-cure testing and treatment are not cost-effective in resource constrained settings, further understanding the biological mechanisms that contribute to persistent infections is imperative.

Table 2. High frequency of persistent STI positivity following standard treatment at Test-of-Cure (ToC), Pretoria, South Africa

	ToC 1	ToC 2	ToC 3
Any STI	36/136 (26.5%)	14/136 (10.3%)	7/136 (5.1%)
CT	27/102 (26.5%)	10/102 (9.8%)	3/102 (2.9%)
NG	1/16 (6.3%)	0/16 (0%)	--
TV	11/66 (16.7%)	5/66 (7.6%)	4/66 (6.1%)

Vaginal microbiota may play an important role in STI treatment outcomes and an important role in genital CT infections.[84-86] Epidemiological studies have demonstrated that BV is associated with an increased risk of acquiring and transmitting HIV and other STIs.[87-95] Culture-independent studies of vaginal bacterial communities have revealed that BV is highly associated with vaginal community state types (CSTs) that are deficient in *Lactobacillus* spp., especially *Lactobacillus (L.) crispatus*,[21,96-98] and that these CSTs are associated with STIs such as CT and TV.[22,23,30] However, there are little data on the role of the vaginal microbiota on CT treatment outcomes in women.

Women with CT are more likely to have vaginal microbiota dominated by *L. iners* or diverse anaerobic bacteria.[22] In addition, risk of genital CT increases during BV episodes.[99] Interferon-gamma (IFN-γ), a host pro-inflammatory cytokine known for its anti-chlamydial properties, is an important part of the host immune response to genital CT infection. IFN-γ activates indoleamine 2,3-dioxygenase in host epithelial cells, which then catabolizes L-tryptophan into N-formylkynurenine. When that happens, the host cell's pool of tryptophan is depleted, which may result in CT eradication by tryptophan starvation. *In vitro*, genital CT strains have been found to rescue themselves by producing tryptophan from indole using a tryptophan synthase gene when indole is present in the local environment.[85] Indole-producing bacteria (e.g., *Prevotella* spp,[85] *Fusobacterium nucleatum*, *Propionibacterium acnes, Porphyromonas gingivalis, Escherichia coli*, and *Enterococcus faecalis*) present in altered vaginal microbiota may contribute to genital CT survival by providing a source of indole. It is currently unknown if treatment for genital CT is inactivated by certain bacteria, or if the presence of indole producing bacteria in an altered vaginal microbiome increase the risk for poor treatment outcomes. Consequently, additional research on the role of the vaginal microbiome in genital CT treatment outcomes is urgently needed, particularly in pregnant women where the adverse effects of CT infection are substantial.

INNOVATION

1) Use of hybrid type 1 effectiveness-implementation study design: A major issue in health care is the relatively slow speed at which promising interventions, supported by rigorous research evidence, move into clinical practice. One way to 'speed up' the traditional step-wise progression from a clinical effectiveness trial to an implementation science trial is to **simultaneously combine the collection of effectiveness and implementation-relevant data**. Toward this end, we will conduct a hybrid type 1 effectiveness-implementation design study,[100] which allows the primary focus to be on collecting data on the effectiveness of our intervention, while also incorporating process evaluation methods into our effectiveness trial. This will help us to explain our effectiveness results and efficiently inform future implementation.

2) Investigating clinical- and cost-effectiveness of routine CT/NG/TV testing of pregnant women: Our study will inform global health practices regarding STI screening during pregnancy, especially among high HIV prevalence populations. We will also assess the effectiveness of routinizing diagnostic testing, with same-day test results and treatment, for in reducing adverse birth outcomes due to these STIs. There have been no RCTs in low and middle-income countries that have evaluated the costs and benefits of diagnostic CT/NG/TV testing and treatment during pregnancy as it relates to birth outcomes. Our cost/cost-effectiveness study has the potential to influence global health policy. If successful, this study would provide reproducible cost-effectiveness analysis models for countries to better plan for and implement routine STI testing and treatment in pregnancy.

3) Prospectively investigating associations between the vaginal microbiome and antibiotic treatment outcomes for STIs: Persistent CT and TV infections not associated with poor medication adherence, re-exposure/ re-infection or drug resistance have been reported.[28,79,81,101-103] Studies have suggested a role for the vagina microbiome in STI persistence, yet to our knowledge, none have prospectively investigated the role of the vaginal microbiome. Our study will longitudinally collect vaginal specimens from both HIV-infected and uninfected women 1) before, during and after antibiotic treatment for STIs, and 2) from those with successful treatment outcomes and treatment failures. This design will allow us to investigate the potential impact of the vaginal microbiome on STI persistence. If specific CSTs are found among pregnant women with persistent *C. trachomatis* infection, these data could be used to identify bacteria that interfere with azithromycin (i.e., CT treatment) and lead to possible alternatives to azithromycin (or co-treatment). Future studies may include trials of adjunctive treatment targeting specific bacteria or CSTs, designed to reduce cost and patient burden.

4) Vaginal microbiome data analysis: Numerous methods are use for sequencing and bioinformatics analysis of vaginal microbiome data.[104] Comparability studies of research methods for 16S rRNA gene sequencing and analysis have been performed by our group[105] and others.[106] Research by our group found that the bioinformatics pipelines to be used by the Taylor lab in Aim 3 (i.e., DADA2,[107] Ribosomal database project (RDP) classifier,[108] and Silva v132 database[109]) provide accurate classification of vaginal bacteria down to the species level. The Taylor lab has also developed methods to visualize changes in the vaginal microbiota over time, including graphic display of microbiome changes via longitudinal heat maps and analysis of CST changes.[110]

APPROACH

Study Setting: This study will take place in Tshwane District, Pretoria, South Africa. Study participants will be recruited from three large ANC clinics (Table 3) located in the referral zone of two **maternal obstetric units (MOUs)**; Kalafong Hospital and Laudium Community Health Centre. Our ANC study clinics and two hospital MOUs were selected due to their association with the South African Medical Research Council's (SA-MRC) Maternal and Infant Health Care Strategies Research Unit (MIHCSRU), directed by **co-I Pattinson**. Kalafong Hospital is co-located with the MIHCSRU and is one of the University of Pretoria's academic hospitals. The MIHCSRU and Kalafong Hospital are two of Africa's leadings centers for maternal-infant health research, with significant research funding and outputs (see Pattinson Letter of Support). The MIHCSRU regularly conducts studies within the two hospital MOUs and catchment area clinics; staff in the two study MOUs are well-trained to complete medical records and optimally collect factors related to birth outcomes consistent with high caliber research (see Dr. Pattinson's biosketch). Ultimately, the selected study sites are outstanding locations in which to conduct this study. Study clinics and MOUs are proximal to and provide care for persons living in informal settlements and lower SES communities. Key ANC indicators for our study clinics are shown in Table 3.

Facility Name	Annual ANC 1st visit headcount	Ave. Monthly 1st ANC Head Count	Annual ANC HIV Prevalence	New HIV diagnosis at 1st ANC (Annual)
Laudium Clinic	2853	238	23.3% (665)	403 (60.7%)
Olievenhout Clinic	1125	94	24.7% (278)	131 (47.1%)
Phomolong Clinic	1323	110	23.1% (306)	129 (42.2%)
Total	5301	442	23.6% (1249)	663 (53.1%)

Table 3: Key ANC indicators for selected study clinics, July 2016 – June 2017

Research Team: Details of the expert team may be found in the biosketches, and in the human subjects attachment highlighting the *Overall Structure of the Study Team*. Of note, Drs. Klausner and Medina-Marino have collaborated successfully on grants, publications, NIH-Fogarty training and infectious disease/ reproductive health projects since first meeting and working together at CDC-PEPFAR South Africa in 2010. Their current successful R21 (2015-2018) from NICHD directly informs this new proposal and resulted in 25 scientific abstract presentations, six publications and additional three recently submitted articles in review.

Preliminary Studies in Support of Aim 1 (All from Medina-Marino/ Klausner NIH R21HD084274):

1) Acceptability/Feasibility of STI testing among HIV-infected pregnant women, South Africa: We enrolled 845 HIV-infected pregnant women attending ANC. Of 442 eligible women offered CT/NG/TV testing using self-collected vaginal swabs, 430 accepted screening (Acceptability= 97.3%).[111] All women had valid test results; >95% received test results within 90 min. Among the 174 women with a positive test result, 92% (n=159) received same-day treatment. *Our results demonstrate that integrating diagnostic testing for STIs into ANC services is acceptable and feasible, and that our study team has the capacity and experience to conduct the proposed study with high enrollment and implementation fidelity.*

2) Test of Cure and treatment outcomes: Among 174 STI-positive participants at first ANC, 78% (n=136) returned for a test-of-cure 3 weeks later. Of those, 26.5% (n=36) had any positive result (CT= 26.5%; TV= 16.7%; NG= 6.3%).[112] Interviews revealed 91.7% of women reportedly disclosed their results to their partner(s), and 64.7% of partners either accepted a partner treatment packet or sought care at a clinic. Interviews suggested

behaviors associated with re-infection or poor medication adherence cannot account for the high persistent positivity after treatment.[113] Those findings suggest that *a single diagnostic test with immediate treatment may not optimally decrease STIs at time of delivery*. Furthermore, *biological mechanisms that increase the risk for STI persistence must be further investigated.*

3) STI incidence during pregnancy and prevalence at time of delivery: Among 430 women tested and treated for CT/NG/TV at first ANC, we identified a 9.1% cumulative incidence of STIs between first ANC and delivery. Furthermore, our screening intervention decreased prevalent STIs by >50% compared to women receiving syndromic management (RR = 0.52; Intervention=11.1%, 95% CI: 7.9%–15.5%; Control=21.2%, 95% CI: 16.7%–26.6%).[112] *While a single molecular test and treatment approach may decreased prevalent STIs at delivery, it cannot identify incident STIs. Optimal, cost-effective screening algorithms are needed to identify incident infections and decrease the risk of sequel associated with STIs in pregnant women and neonates.*

4) Linkage and utility of national databases for data optimization: We captured unique bar codes of all requested laboratory tests and used this to query the National Health Laboratory Service (NHLS) lab information system (LIS) for maternal syphilis, CD4, HIV viral load, and infant HIV PCR results. Of those tested, we were able to obtain results for 87% of all syphilis tests (1.2% prevalence) and 100% of infant HIV PCRs (0.6% positivity). For those with CD4 and HIV viral load test results not recorded in medical charts, we obtained 85.4% and 80.5% of missing values, respectively, using both the NHLS-LIS and National HIV database (Tier.Net). *We will similarly leverage the use of national datasets to ensure completeness of all study variables.*

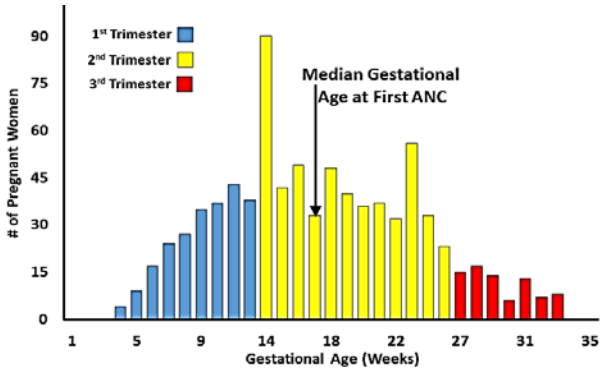


Figure 1: Gestational Age at First ANC Visit among HIV-infected Pregnant Women, Tshwane District, South Africa

5) Gestational age at first ANC and MTCT of STIs: Median gestational age was 17 weeks (IQR 12-22 weeks; Figure 1). In sub-analysis of 430 intervention arm women, enrolling in ANC during the 3rd trimester was associated with a higher prevalence of any STI compared to those who enrolled earlier.[19] Neonates born to mothers who enrolled for ANC during the 3rd trimester had significantly higher risk of nasopharyngeal colonization with maternal STI organisms compared to those whose mothers enrolled earlier (aPR=2.56; 95% CI: 1.22 – 5.38). *Those findings support our decision to not include gestational age as inclusion/ exclusion criteria.*

Preliminary Studies in Support of Aim 2:

6) Cost-effectiveness modeling for ANC STI interventions (Klausner; P30MH058107): In Botswana, we conducted micro-costing, including time-and-motion studies and provider interviews, to identify capital and recurrent costs of antenatal STI testing interventions, compared to syndromic management. By combining those data with population and epidemiological data from Botswana, and probabilities from the literature, we developed a decision model comparing three approaches for national scale-up of STI testing. Our model revealed that a mixed approach to scale-up, including both PoC and centralized testing, had the lowest cost per STI treated.[114] By extending our model to include health outcomes (i.e., maternal infections at delivery, low birth weight infants, and DALYs averted), our model showed that, *diagnostic testing for STIs during ANC services can be cost-effective if policy makers are informed by the WHO Gross Domestic Product / capita threshold. However, identifying the most cost-effective testing algorithms require further research. This work also shows that our study team has the capacity and experience to conduct the proposed study.*

Preliminary Studies in Support of Aim 3:

7) Vaginal microbiome of HIV-negative South African women (Meiring; SA-NRF 13100150715/91478): We recently completed a study assessing the association between the vaginal microbiome and prevalent human papillomavirus (HPV) infection in 87 reproductive age HIV-negative Black South African women. A minority of the women (N=23, 26.4%) were found to have *Lactobacillus* spp. dominant vaginal microbiota; two (2.3%) were CST I, *L. crispatus* dominated; two (2.3%) were CST V, *L. jensenii* dominated; 19 (21.8%) were CST III, *L. iners* dominant; zero were *L. gasseri* dominant. The majority of women (n=64, 73.5%) had diverse vaginal microbiota with low to no *Lactobacilli* spp. present and complex mixtures of BV-associated bacteria. *Gardnerella vaginalis*, *Atopobium vaginae* and *Sneathia* were identified as putative biomarkers for prevalent hrHPV (manuscript in preparation). *This work provides insight into the structure and composition of the vaginal microbiome of HIV-uninfected South African women, and can provide a useful comparison for our proposed study.*

8) Pathogenesis of BV in African American women who have sex with women (Muzny; K23AI106957). We followed women prospectively for **incident BV** (**iBV**; Nugent score 7-10, at least 2-3 consecutive days) with

daily self-collected vaginal swabs for 90 days. For women with iBV or maintaining normal vaginal flora (NVF), we performed 16S rRNA sequencing targeting V4 was specimens for 21 days prior to iBV; raw MiSeq reads processed via DADA2. Species-level taxonomy was assigned to variants using PECAN[110] and merged with RDP assigned taxonomy using GreenGenes13_5. Longitudinal microbiome data for BV-candidate bacteria and lactobacilli of interest were analyzed using phyloseq library. Of 31 participants completing the study, 14 (45.2%) developed iBV; 448 specimens were sequenced (14 women with iBV; 8 women maintaining NVF). Relative abundance of *G. vaginalis, P. bivia, A. vaginae*, and *Megasphaera*-type1 became significantly higher in women with iBV 4 days before, 3 days before, and day of iBV (*A. vaginae* and *Megasphaera*-type 1), respectively.[110] *Novel methodologies from this study will be incorporated into Aim 3.*

9) Consequences of the vaginal microbiota on IFNγ-mediated clearance of *Chlamydia trachomatis* (CT) (Taylor; 1R01AI118860-01A1). We are assessing the influence of the vaginal microbiota on the incidence of CT clearance without treatment. Vaginal swabs from women with persistent or spontaneous CT clearance are 16S rRNA gene sequenced, targeting the V4 region, and DADA2 pipeline processed and taxonomy is assigned using the RDP classifier[115] and silva version 128 database.[116] Preliminary results show a prevalence of indole-producing microbiota in the vaginal microbiome of women with persistent CT infection, and a lack of indole-producing microbiota in women who cleared infection without treatment. *Those results further support our rationale for studying the vaginal microbiome in pregnant women with persistent CT infections.*

10) Effect of BV on CT organism load and treatment outcomes (Muzny; U19AI113212). We are investigating the relationship of BV with 1) CT organism load, and 2) time to CT DNA clearance after treatment with 1g azithromycin in non-pregnant CT-infected women. To date, 17 CT-infected females have been assessed. We have found a general trend towards a longer median CT DNA clearance time in women with BV (2 days longer, p=0.286); when G. vaginalis and other anaerobic gram-negative rods are seen on Gram stain, 3 days longer (p=0.221); with lactobacilli not seen on Gram stain, 7 days longer (p=0.155); and with a vaginal pH >5, 3.5 days longer (p=0.123).[115] Higher vaginal pH correlated with higher baseline log10 CT load (p=0.0352), with a trend in higher Nugent score correlating with higher baseline log10 CT load (p=0.114). *Those preliminary data suggest that women with altered vaginal microbiota take longer to clear their CT infection, supporting our aim to investigate the role of the vaginal microbiome in persistent CT infection among pregnant women.*

METHODOLOGY AND STUDY AIMS

Specific Aim 1: Evaluate different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes

Aim 1 (Figure 2) will achieve three main sub-aims: **1(a)**: compare the effectiveness of multi-timed PoC diagnostic screening (Arms 1+2 Treatment Groups) to one-time diagnostic screening (Arm 3; Active Control) in reducing the frequency of adverse birth outcomes (e.g., preterm delivery, low birth weight, stillbirth/miscarriage); **1(b)**: compare the effectiveness of single point-in-time diagnostic screening with targeted treatment plus test-of-cure (Arm 1 Treatment Group) *vs* repeated diagnostic screening throughout ANC and treatment without test-of-cure (Arm 2 Treatment Group) in reducing prevalent and incident STIs at time of delivery; **1(c)** collect process measures to inform future implementation and scale-up.

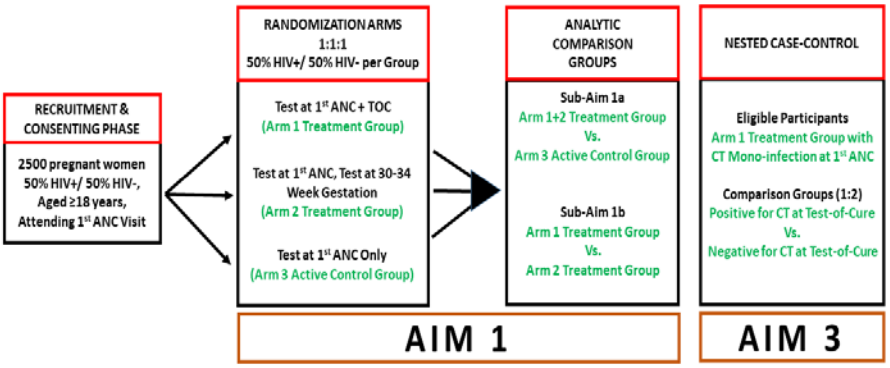


Figure 2: Study Diagram for Aim 1 Randomization Arms and Analytic Comparison Groups, and Aim 3 Nested Case-Control Study

To achieve Aim 1, we will conduct an effectiveness-implementation hybrid type 1 three-arm RCT, with **individual participants randomized (1:1:1)** from within each clinic to one of the following arms: **Arm 1 Treatment Group:** single point-in-time molecular PoC diagnostic screening and treatment for CT, NG and TV at first ANC visit and infection-specific test-of-cure 3 weeks post-treatment. Women with a positive test-of-cure will be re-treated and requested to return every 3 weeks for follow-up visits until a negative test-of-cure result or birth outcome is documented. **Arm 2 Treatment Group:** repeated molecular PoC diagnostic screening and treatment for CT, NG and TV at first ANC visit and week 30–34 gestation. No test-of-cure will be conducted for women with positive test results. **Arm 3 Active Control Group:** one-time diagnostic screening at first ANC visit, with targeted treatment but no follow-up ToC or repeat testing. Arms 1 and 2 are the intervention arm, Arm 3 is the comparison arm.

Of particular note, syndromic management is the standard of care in all low and middle-income countries. However, our previous work revealed that 64.9% of women were asymptomatic, thus leaving a large proportion of pregnancies and infants at risk for an adverse outcome from STIs. As such, the equipoise of retaining syndromic management standard care as the comparison arm necessitates an active control that includes once off diagnostic testing at first ANC visit (Arm 3).[117,118]

Recruitment and Eligibility: We will recruit 1250 HIV-infected and 1250 HIV-uninfected pregnant women presenting for ANC services at our 3 study clinics in Tshwane District, South Africa. Eligibility criteria: 1) Age ≥18 years, 2) Currently pregnant, 3) Attending first ANC visit for current pregnancy, 4) Willingness to self-collect up to four vulvo-vaginal swabs, 5) Residence in Tshwane District, and 6) Intent to stay in Tshwane District through delivery. Gestational age will NOT be used as an inclusion/exclusion criterion, as a substantial proportion (30%) of South African women enroll for ANC late in pregnancy (Fig 2). Further, inclusion of pregnant women across gestational ages will enable us to assess optimal timing for screening to prevent adverse birth outcomes.

All pregnant women will be screened for eligibility by study staff following standard HIV testing per South African National Guidelines.[119] Study staff will be trained in the study's methods, protocol, and human subjects research, and will receive training on South Africa's syndromic management algorithms for STIs. Staff will read all eligible women a brief study description. Interested women will then be read aloud, in their preferred language, the study consent form and will be invited to participate. Those providing informed consent will be enrolled and randomized into one of the 3 study arms; randomizations will be allocated in blocks of 12 with a 1:1:1 randomization into the 3 study arms. Prior to enrollment, each clinic will be provided two unique simple random allocation lists in Microsoft Excel, one for HIV-infected participants and one for HIV-uninfected participants; each study arm will be composed of 50% HIV-infected participants (purposive enrichment). While the impact of our intervention on prevalent STIs at time of delivery should be valid regardless of HIV-infection status, work by our group has shown maternal HIV infection is associated with increased adverse birth outcomes regardless of antiretroviral therapy (ART), CD4 count, or HIV viral load.[120] Given the complex interplay between HIV status and adverse birth outcomes, and the fact that approximately one-third of pregnant women in South Africa are HIV-infected, it is essential to demonstrate the impact and investigate the effect size of our proposed interventions on adverse birth outcomes among both HIV-infected and un-infected women.

Staff will record reasons for ineligibility/refusal. Basic de-identified information (i.e., age, gestational age, HIV/ART status) will be collected from clinic logs for descriptive analysis of the general ANC patient population.

Data Collection at Enrollment/First ANC: Trained study staff will administer an audio-computer assisted self-interview (ACASI)-based questionnaire to all participants. The ACASI questionnaire, adapted in part from measures used by our team in previous and current STI screening and maternal-child health studies, or documented in the literature, will include participant: 1) demographics and socio-economic status, 2) obstetric, gynecological and sexual health history, 3) sexual behaviors, risk factors and self-perception of risk for HIV and STI acquisition before and during pregnancy,[121] 4) partner characteristics and HIV status,[122,123] 5) knowledge and previous history of STIs, and 6) screenings for depression,[124,125] substance abuse,[126] interpersonal violence and social support. Staff will translate questionnaires into the major local languages (i.e., Sepedi, Setswana, Zulu, and Ndebele). Participants may select their preferred language for the ACASI questionnaire, but will also be able to toggle between languages during the questionnaire to ensure linguistic comprehension of all questions. Staff will abstract additional clinical history from each participant's maternity case record, including HIV status, date of diagnosis, and immunological characteristics associated with HIV infection (e.g., CD4 T-cell level, HIV viral load, ART use/duration). The maternity case record is used from the day of first ANC consultation to record clinical information throughout the duration of the pregnancy. Staff will verify self-reported and medical record-abstracted HIV-related information with data from the South African national HIV database, Tier.net, and the South African NHLS corporate data warehouse, both of which contain individual-level heath data.

Specimen Collection, Handling, Transport and Storage: Consenting participants will be instructed on how to self-collect a vulvo-vaginal swab specimen and asked to provide up to four swabs: 2 swabs for STI testing, 1 swab for microbiome analysis (Aim 3), and 1 swab for bio-banking (NOTE: all pregnant women from our recently completed study found it acceptable and feasible to collect up to four vaginal swabs at a visit). Vaginal pH of participants will be measured on pH strips using vaginal secretions collected from a swab used for STI testing; pH strips will be interpreted using the manufacturer's chart.[127] If a participant is not comfortable with self-collecting a vulvo-vaginal swab they will be given the option to provide a urine specimen for testing and bio-banking (women that only provide urine specimens for testing will not be included in the cohort for microbiome analysis, Aim 3). Staff will handle specimens and label with a unique study barcode to link a participant's STI test results, medical chart and questionnaire data (see *Data Collection*). Participants will use the GeneXpert Vaginal/ Endocervical Specimen Collection kit [Cepheid, Sunnyvale, CA] for vaginal swab specimen collection.

For vaginal microbiome analysis, participants will use a Dacron swab [Qiagen, Digene] for self-collection, with subsequent storage in DNA AssayAssure® [Sierra Molecular, Incline Village, Nevada] at ambient room temperature. For specimen bio-banking, participants will use a dry FLOQswab® [COPAN, Murrieta, CA] for specimen collection, with subsequent storage in a sterile tube. Collection of vaginal swabs for microbiome analysis and bio-banking (Aim 3) will occur before any STI treatment. Specimens will be stored at 2-8°C and transported to **Dr. Peters** (co-investigator; Dept. of Microbiology, University of Pretoria) on a bi-weekly basis according to Good Laboratory Practice. Specimens will be flash frozen and stored at -80°C for bio-banking. Frozen specimens will be shipped quarterly for microbiome processing and analysis to University of Cape Town.

Diagnostic Testing: Vaginal specimens collected from participants will be tested for CT, NG and TV using the Xpert® CT/NG and Xpert® TV assays [Cepheid, Sunnyvale, CA]. Trained staff (STI Test Counselors and Research Nurses) will conduct the PoC testing at each of the clinical sites. Once collected, research staff will follow test kit instructions for swab preparation and testing. Xpert® CT/NG provides 90-minute detection and differentiation of CT and NG, while Xpert® TV provides 60 min detection of TV; both test cartridges have high sensitivity and specificity[127] and function well in resource-constrained environments and clinical settings such as those proposed here. Each test includes a sample processing control (SPC) to ensure correct cell lysis/DNA extraction of the sample, a sample adequacy control (SAC) which ensures adequate human DNA in the specimen and a probe check control (PCC). The PCC monitors reagent rehydration, reaction-tube filling, probe integrity, and dye stability. If testing cannot be conducted due to power failures, errors, or testing delays, specimens will be stored at 2-4°C in a secure storage area for up to 24 hours until tested.

Testing, Reporting and Treatment: The GeneXpert systems consist of an instrument, computer, and preloaded software for running tests and displaying results. STI Test Counselors will report all test results to the ANC Research Nurse embedded within study clinics. Research nurses provide test results notification, treatment, partner treatment counseling and treatment packets to STI-infected participants per National STI treatment protocols.[128,129] Arm 1 and 2 participants will be provided same day results and immediate treatment. Arm 3 participants will be provided results and treatment at their routine follow up ANC visit; reporting of results and provision of treatment at a woman's 2nd routine ANC is in line with South African guidelines for syphilis test result reporting and treatment provision, thus better approximating a likely future scenario.[128,129]

Partner Treatment: Women testing positive for an STI will be counselled on safe disclosure to their partners, assessed for potential intimate partner violence related to disclosure, and given the option to either request their partner(s) present to a clinic for treatment, or be given an infection-specific partner treatment packet of oral medication to take to their partner(s). Targeted treatment for partners will be provided according to the South African STI National Guidelines; in lieu of the recommended intramuscular injection of ceftriaxone for NG infections, which would require a male partner to present to a clinic, WHO and South African National Guidelines recommend oral Cefixime 400mg tablet/ azithromycin 1gm oral to be administered for NG infection.[128,130] Partner treatment will be placed inside a small yellow envelope labelled with the medication name, dosage, instructions, expiration date, and lot number. This manner of providing partner treatment was found to be highly acceptable and feasible in our R21 study. Several mechanisms will be used to ascertain that partners sought care or actually took medication provided via partner pill packets: 1) women will complete a questionnaire during the test-of-cure visit, with questions about whether their partner(s) sought care at a clinic or swallowed pills from the treatment packet, 2) partner referral letters will detail a fast track servicing by research nurses should they wish to receive STI treatment at one of the three study facilities, and 3) participants consent to study staff contacting their partner, and the partner verbally consented to a brief telephonic interview regarding STI treatment behaviour. Partner interviews will include: 1) assessment of disclosure dynamics; 2) determination of receipt and self-administration of partner treatment packet; 3) preference for partner treatment packet vs. attending clinic for care; 5) knowledge, attitudes, practices regarding STIs; and 6) STIs in their pregnant partner and their own health. Characteristics of contacted partners may be biased given that women who provide consent for contacting may have differential partnership dynamics indicative of particular health behaviors in these partners.

Arm 1 Specific Activities: Per Table 4, at first ANC visit, participants randomized to Arm 1 will collect four vaginal swab specimens as described above (*Specimen Collection*). Two specimens will be used for pH, CT/NG and TV testing, and two for bio-banking. Test of Cure (ToC): Participants treated for an STI infection at first ANC will be asked to return 3 weeks post-treatment for a targeted ToC (i.e., women will only be tested for the STI for

Table 4: STI Testing Schedule Per Randomization Arm

Clinic Visit	Participant	Specimen Collected	CT, NG and TV Testing
First ANC Visit	**All Pregnant Women**	**Vaginal Swabs**	**All Arms**
ToC 3-Weeks Post-treatment	**Arm 1 Only**	**Vaginal Swabs**	**Arm 1 Only**
30 – 34 Weeks Gestation	**Arm 2 Only**	**Vaginal Swabs**	**Arm 2 Only**
First Post-delivery Clinic Visit	**All Post-partum Mothers**	**Vaginal Swabs**	**All Post-partum Mothers***
First Post-delivery Clinic Visit	**All Infants**	**Nasopharyngeal Swab**	**All Infants***

***Post-delivery maternal and infant swabs will be batch tested at the end of the study**

which they were treated). At the ToC visit, women will again self-collect vaginal specimens for STI ToC and bio-banking. Women with positive ToC will again be treated (and given partner treatment packet) and asked to return 3 weeks later for another ToC; ToC will be repeated until negative test result or documented birth outcome.

Arm 2 Specific Activities: Per Table 4, at BOTH at first ANC visit and during ANC visit occurring between 30-34 weeks gestation, participants randomized to Arm 2 will collect four vaginal swab specimens; two for pH, CT/NG and TV testing, and two for bio-banking. No ToC activities will be performed for Arm 2 participants.

Arm 3 Specific Activities: Per Table 4, at first ANC visit, participants randomized to Arm 3 will be asked to collect four vaginal swab specimens; two for pH, CT/NG and TV testing, and two for bio-banking. Reporting of test results and provision of treatment (self and partner) for those with a positive STI result will be provided at a women's next routine ANC visit.

Retention and Follow-up: To ensure retention, those providing informed consent will be asked to provide detailed contact information (e.g, phone numbers and home address for self, family, friend/neighbor). To develop and maintain a strong relationship with participants, study staff will conduct welcome phone calls within 3 days of enrollment, and check in with participants during regular ANC clinic visits or monthly ART pickup for those with HIV. We will flag participant charts so that clinic staff will notify study staff on date of delivery. Seven days post-delivery, study staff will contact participants not yet attending a first postnatal clinic visit to schedule an outcomes interview. We will make up to 7 attempts to follow up with participants via text/phone call/home visits.

Element	Questions	Measures	Data Sources/Tools
Reach	1) What % of eligible patients consented to receive the intervention? 2) Do those that consent differ significantly from those that do not?	1) Recruitment rates 2) Socio-demographics of all eligible participants stratified by consent/refused	1) Enrollment tracking sheets 2) Enrollment tracking sheets
Effectiveness	What is the effect of the intervention on patient outcomes?	Main study outcomes comparing interventions & Control	Study datasets
Adoption	1) What are the main barriers/facilitators to adopting the intervention? 2) What systems need to be in place for the health system to adopt intervention?	1) Perceptions of research/clinic staff, facility management, NHLS & NDoH	1) Staff observational logs and post-intervention interviews 2) Post-intervention interviews clinic and national stakeholders
Implementation	1) What does the intervention cost? 2) What support and tools are needed for consistent delivery of intervention?	1) Cost/Cost-effectiveness data 2) Perceptions of study and clinic staff, NHLS and NDoH	1) Study datasets 2) Post-intervention interviews w/ clinic & national stakeholders
Maintenance	1) What resources will be needed for the intervention to be sustainable? 2) What adaptions are needed to integrate intervention into current practices?	1) Perceptions of research staff, facility managers, NHLS and NDoH	1) Research staff observation logs, post-intervention interviews 2) Post-intervention interviews clinic and national stakeholders

Table 5: RE-AIM Conceptual Framework Guiding Process Evaluation (adapted from Hagedorn *et al.*[121])

Post-partum and Infant Specimen Collection: During the first postnatal visit (typically 3-6 days post MOU discharge), four vaginal swab specimens will be collected from all post-partum women and two nasopharyngeal (NP) swabs specimens will be collected from all infants. Specimens will be labeled with random specimen IDs that link to participant IDs. Specimens will be transported to the Univ. of Pretoria and stored as previously described. Vaginal and NP swabs will be batch tested using Xpert® CT/NG and Xpert® TV assays at study end. Test results from all participants will be used specifically for study outcomes, not clinical management.

Data Collection at Postnatal Clinic Visit: We will collect data on pregnancy and birth outcomes from all study participants via abstraction of labor/postnatal ward clinical records and face-to-face interviews with participants during the first postnatal clinic visit. All clinical data relating to labor, delivery and birth/neonatal outcomes are recorded on a discharge summary; women are given a copy of discharge summaries when they leave an MOU (a carbon copy is kept in the labor ward). Additional data will be abstracted from the infant health record, known as the Road-to-Health card, which is issued to all infants born in South African facilities. Staff will collect information on fetal loss, preterm labor, preterm birth, birth weight, the calculated small-for-gestational-age status, and infant mortality. Information on potential confounding variables such as maternal history of chronic illness (e.g., hypertension, diabetes), other infections during pregnancy (e.g., urinary tract infections, syphilis), antibiotic use during pregnancy, and pregnancy complications (e.g., premature rupture of membranes, maternal fever, chorioamnionitis, and pre-eclampsia) will also be collected. HIV PCR results from routine at-birth testing of HIV-exposed infants will be collected via clinical records, and verified using the South African NHLS database. At the routine 6-week immunization visit, we will assess for neonatal health outcomes and morbidities (or mortality) (i.e., respiratory distress, conjunctivitis, sepsis) via maternal interviews and patient medical records. Should a mother-infant pair not present for a scheduled 6-week follow up visit, research staff will make repeated attempts to provide assistance to attend clinic. If neonatal mortality is identified, a verbal autopsy will be

performed, and death will be confirmed via medical records. A study supervisor will perform weekly reviews to ensure data completeness and validity; discrepancies will be resolved via interview with the birth attendant.

Data Collection for Process Evaluation: We will use the **R**each-**E**ffectiveness-**A**doption-**I**mplementation-**M**aintenance (RE-AIM) model as our **conceptual framework**[131-133] to guide the collection of valuable information during our effectiveness trial. Per Table 5, a mixed methods approach will be used to collect process measures such as recruitment rates, refusal characteristics, perceived and experienced barriers and facilitators to optimal implementation, intervention costs, impact of intervention on patient outcomes, perceived health system readiness to implement our interventions, and to assess modifications that can be made to maximize future implementation success. We will extract quantitative measures from implementation tracking tools, recruitment/refusal logs, participant demographic data, and participant tracking/retention tools. Qualitative data will be collected during interviews with different stakeholders, including participants, research and clinic staff, facility managers, and the South Africa NHLS and National Department of Health (NDoH).

Data Analysis: Data will be analyzed using R [R Foundation for Statistical Computing, Vienna, Austria] and SAS 9.4 [Cary, North Carolina]. Participant demographic and clinical characteristics will be described per study arm using proportions (categorical variables), as well as measures of central tendency (sample mean, sample median) and dispersion (sample variance, interquartile range) for continuous variables. Outcome difference among treatment arms will be assessed for statistical significance using Chi-square tests and logistic regression models for categorical/binary outcomes. Analysis of Variance (ANOVA) and multiple linear regression models will be used for continuous outcomes. Normal probability plots will be used to access the normality assumption for ANOVA and multiple linear regression models. If the normality assumption appears violated, non-parametric procedures will be utilized. Within Arm 1, we will use 95% confidence intervals for proportions to estimate the percent of women with a negative ToC, but with an STI at birth outcome. These confidence intervals, calculated by HIV status as well as pooled across HIV status, will allow an estimation of the percent of STI prevalence at birth outcome which is due to new infections between ANC visits. 4) Within Arm 2, a logistic regression model will be developed utilizing incident STIs (negative at first ANC visit, positive at 30-34 week ANC) to determine if there is an optimum gestational age at which a second STI screening would be most beneficial or if the data indicates a steady probability across gestational ages.

All analyses will be conducted using intent-to-treat principles. Overall Type I error rate will be set at 0.05; for multiple comparisons among study arms Type I error will be set to a Bonferroni-corrected Type I error of 0.01667. We will use multiple imputation of missing data when missing values exceed 10%, and will conduct sensitivity analyses to determine how imputed data affects the study results.

Primary Outcomes to be compared among study arms, adjusted/controlling for HIV status include: 1) frequency of adverse birth outcomes (sub-Aim 1a) and 2) change in STI prevalence between baseline (1st ANC) and birth outcome). We will calculate the change in CT, NG, and TV prevalence by subtracting the prevalence at delivery from the prevalence at baseline. We will use generalized estimating equations to test for variation among study arms with regard to change in prevalence of CT/NG/TV between baseline and delivery, adjusting for potential effect modifiers and confounding variables. Secondary Outcomes: 1) prevalence and risk factors for CT, NG, and TV colonization in neonates controlling for HIV status; 2) among mothers, the prevalence and risk factors for STI infection at birth outcome, 4) factors associated with STIs at first ANC; and 5) process evaluation measures as described in Table 5. Exploratory Outcomes: 1) type and frequency of adverse birth outcomes as a function of STI and HIV status; 2) infant outcomes, including pneumonia and neonatal conjunctivitis, at 6 weeks.

Development of persistent STI risk score calculator: We will use a predictive modelling approach to develop a STI risk calculator.[134] To assure model utility, we will select variables that are readily available to clinicians *a priori*. Model building will utilize 10-fold cross validation where the data is randomly divided into 10 datasets. For each model fitting iteration, 9 of the datasets will be used to fit the model. This resulting model will then be used to predict outcome in the 10th dataset. The final model will be a weighted average of the models observed in each of the 10 cross-validation steps. Weights will be assigned based upon observed degree of fit with models exhibiting higher degree of fit (better prediction) receiving higher weights. To assess external validity of the model, the model will be applied to the dataset from our prior study (R21HD084274). Risk calculators will be developed for any STI as well as separately for CT, NG, and TV.

Analytic Plan for Process Evaluation Qualitative Data: We will employ aspects of deductive analysis that take into account the RE-AIM framework through the creation of initial *a priori* codes. Data coding and analysis will be an iterative and interactive process. Interview transcripts will be read to increase familiarity with data. *A priori* and emergent codes will be assigned. Transcripts will be re-read to create pattern codes that connect subsequent concepts under larger headings. Consistent patterns in meaning, concepts, and themes across interviews will be identified, and data matrices created as visual representations of findings.[120,133,135] We will also examine any

differences based on stakeholder type (i.e., study staff, non-study clinic staff, NHLS and Health Department) to identify unique viewpoints. Coding and analytic activities will be discussed during qualitative data analysis meetings; discrepancies in coding and interpretation will be resolved through consensus.

Potential Challenges and Quality Assurance: Loss-to-follow up, postnatal specimen collection and interviews, and adequate 6-week infant follow-up visits may be the dominant Aim 1 challenges. In our current R21 study, optimized retention strategies resulted in >85% retention. Strategies included enhanced participant tracking, welcome phone calls, employing a community-based roving nurse that visited women in their homes for follow-up visits, and telephonic interviews to collect self-reported outcomes data. We will also hire a midwife research assistant with full access to MOUs to collect maternal and neonatal specimens, and abstract medical records and discharge summaries. Based on current experiences, we believe that we are well prepared to overcome typical retention challenges. Given that syndromic screening/management is performed at all ANC visits, we will abstract medical records of all participants to determine if syndromic management was conducted outside research study events. We will take such events into consideration when analyzing and interpreting our results. Finally, all research study personnel will meet weekly to review study enrollment, specimen collection, processing, test turn-around-time, data management, and treatment outcomes. Meetings will discuss descriptive study results to date, problems encountered and remedial actions to be taken.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and DALY averted.

Rationale: While Aim 1 will determine the efficacy of screening interventions in improving birth outcomes for pregnant women, Aim 2 will assess whether Arms 1 and/or 2 are cost-effective in comparison to Arm 3, from the societal (government provider and patient) perspective.

Data Collection: *The Provider Perspective*: We will assess the full economic costs of each study arm and the full economic costs of adverse birth outcomes. A full economic costing approach includes financial and opportunity costs, and is necessitated by the reality of severely constrained capacity within the South African and similar low/middle-income country health systems. Our approach to costing establishes the utilization of health services (e.g. diagnostic and treatment visits), diagnostic tests, and medication directly from trial data specific to each arm. Within a decision analytic modeling framework, those utilization estimates are multiplied by the full economic or unit cost of each service, diagnostic test or medicine. Unit costs are computed using a combined bottom-up and step-down approach, as appropriate. For example, for diagnostic visits, bottom-up costing captures staff time for diagnosis (using time and motion tools), while step-down approaches are used to apportion shared costs within the facility such as managerial, clerical, cleaning and security staff, and utilities. For diagnostic tests, bottom-up costing is used to capture the costs of the test cartridges and GeneXpert machines (appropriately annuitized). Similarly, the costing of adverse pregnancy or birth outcomes entails the bottom-up costing of clinical staff, infrastructure and equipment within the facility where care is provided (e.g. neonatal ICU), together with a step-down allocation of shared costs such as overheads within the hospital. When valuing resources within the cost analysis that are paid from the research budget, we will use routine public sector 'prices' for staff and medication and will seek to cost GeneXpert machines and cartridges at a level commensurate with a potential public sector scale-up. Care will be taken to exclude any costs that are incurred only as part of research activities. ***The Patient Perspective*:** We will collect demographic, socio-economic, patient cost and household income data. Data will be collected at each interview unless the variable is expected to stay constant over the study period (e.g. educational status). Socio-economic status will be computed via a multiple correspondence analysis on household type, assets, and access to services following established methodology.[120,135] Patient costs will include transport costs, opportunity costs of travel, waiting and visit times, and other out-of-pocket payments, such as user fees (applicable for public inpatient care in South Africa but not for ANC). Productivity gains or losses will not be included, as the study population includes pregnant women and their babies. To increase response rates, questions about household income will include quantitative and categorical approaches.[120] The categorical income variable will be transformed into a quantitative variable using a regression methodology, where household income can be predicted as a function of demographic and socioeconomic status. Per capita household income will be computed as total household income divided by total number of household members, with appropriate adjustments for children. The opportunity cost of time can be valued using wages/salary earnings foregone.[136] In order to value these costs equitably, the mean per capita household income reported at the baseline interview will be used as a proxy of this opportunity cost. In contrast, time, travel and user fee costs will be compared to the mean per capita income of the respondent's own household in order to assess the share of per capita household income spent on these costs.

Decision Analytic Modeling: We will build a decision analytic model to estimate costs and outcomes for each study arm and perspective (provider/patient). Box 1 (see *Statistical Design and Power*) summarizes

formulae for calculating costs and DALYs for the provider perspective (arguably the more complex calculation). For DALY calculations, years of life lost are the difference between age at death and average South African life-expectancy for that age; years of life with disability and disability weights will be estimated from the Global Burden of Disease studies.[137,138] Deterministic sensitivity analyses will assess the impact of key parameter uncertainty (e.g. cost of GeneXpert machines within a scale-up scenario). Probabilistic sensitivity analysis will assess uncertainty around each utilization estimate from the trial.[139] If Arm 3 costs (hypothesized to include higher costs for adverse pregnancy and birth outcomes) are greater than Arm 1 or Arm 2 costs, the intervention(s) are cost-saving and no further analysis would be required. However, if we find that the costs of Arms 1 and/or 2 exceed the costs of Arm 3, we will compute incremental costs per STI and DALY averted. For the patient perspective, catastrophic expenditure will be computed by comparing patient costs to household expenditure using 10% and 20% thresholds per other South African and low and middle-income country studies.[120]

Potential Challenges: The main challenge of Aim 2 involves accurate data collection of newborn hospital care costs, particularly those costs incurred by any higher-level neonatal care. If necessary, we will extend our follow-up of these infants beyond 6 weeks postpartum and will collect newborn cost data until discharge or death, whichever comes first; this will likely be a few months of hospital care for babies born very pre-term.[140-144]

Specific Aim 3. Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women.

Methods and Procedures: For Aim 3, we will conduct a nested case-control study (1:2) using selected bio-banked vaginal specimens collected from participants enrolled and randomized in Aim 1 (Figure 2). We will accomplish two main sub-aims: 3(a): determine the impact of vaginal microbiota on CT treatment outcomes; and 3(b): explore the natural history of the vaginal microbiome in the context of antibiotic treatment for CT infections.

Recruitment and follow-up visits: Participants randomized into Arm 1 of Aim 1 who test positive for a CT mono-infection during their first ANC visit will be invited to participate in a weekly vaginal specimen collection activity until a negative ToC result or a birth outcome is documented. Participants with multiple STIs will be excluded from this sub-study, as the presence of TV and NG may also alter vaginal microbiota.[145-147]

Specimen collection, handling and shipping: The Laboratory of co-I Peters will use the swab collected for bio-banking to smear a glass slide for Nugent score and determination of BV prior to its storage.[148] At week 1, 2 and 3 (i.e., ToC visit), vaginal specimen collection for microbiome analysis, glass slide smearing for Nugent scoring and specimen bio-banking will occur. At ToC, participants will be repeat CT-tested (Aim 1: *Diagnostic Testing* section). Those with positive CT test results at ToC will again be treated with azithromycin 1g, provided a partner treatment packet and asked to return for subsequent weekly specimen collection (weeks 4 and 5) and ToC2 (week 6). Specimens will be collected and stored as previously described.

Nugent scoring for BV: Air-dried slide smears will be heat-fixed and Gram stained per standard procedure.[149] Nugent scores (0-3: normal, 4-6: intermediate and 7-10: BV flora[148]) will be recorded in a laboratory-based data system (REDCap) and linked to a participant's metadata via their unique study ID.

Selection of Stored Specimens for Nugent Scoring and Vaginal Microbiota Analysis: "Cases" will be defined as participants who test positive for CT by GeneXpert at first ANC visit (week 0) and at ToC visit (week 3; 'no clearance'). "Controls" will be participants who test positive for CT by GeneXpert at first ANC visit (week 0) but test negative at ToC (week 3; 'clearance'). The four stored vaginal swab specimens (weeks 0-3) from cases and controls will be selected for Nugent scoring, and along with weekly vaginal swab specimens from "cases" who remained persistently CT positive at first ToC, will also be selected for vaginal microbiota analysis.

Molecular Methods/Interpretation of Sequence Data: Vaginal swabs will be subjected to sequencing of the V4 hypervariable region of the 16S rRNA gene using the well characterized 515F/805R primers; Illumina sequencing primers typically produces amplicons of ~290-292 base pairs. Paired end sequencing using an Illumina V2 sequencing kit 2x250bp produces reads with significant overlap, which will be processed through the DADA2 pipeline to assign high quality sequence variants. Taxonomic classification will be performed using the RDP classifier and silva version 128 database for precise assignment of taxonomy. Phyloseq[150] and QIIME[136] analysis packages will be used to assess taxonomic composition, and alpha and beta diversity of vaginal microbiome communities. Vaginal CSTs will be formed using the Phyloseq package based on hierarchical clustering of samples using Bray-Curtis distance.[151]

Estimated effective sample size: Based on 834 pregnant women randomized to Arm 1 (see *Sample Size Calculations*), and a 30% CT prevalence among pregnant women (Table 1), ~246 CT infected women will be included in Aim 3. Considering 26.5% of CT-infected women had a positive ToC (Table 2), we anticipate approximately 65 "cases" and 130 "controls" (1:2 match). Furthermore, given that 7.9% of CT-infected women may still be positive for CT at the second test of ToC (week 6), 5 women will continue to collect weekly vaginal specimens. Given that each participant will have 4 stored specimens, ~800 vaginal specimens will be sequenced.

Data analysis and statistical considerations: We will analyze associations between Nugent scores, vaginal CSTs, CT treatment outcomes, vaginal pH and other clinical data. We will compare the relative abundance of microorganisms between cases and controls to determine which organisms are associated with persistent CT infection in pregnant women. Several statistical methods have been proposed to evaluate differential abundance in microbiome data (DESeq, DESeq2, and Voom).[152-154] We propose to use the DESeq2 method, which is based on the negative binomial Wald test, as it provides increased sensitivity and several desirable characteristics compared to other competing methods.[155] Data will be analyzed at 4 time points, correlating to specimen collection (see above). Preliminary analysis at each time point will account for individual effects of different microbiota at different study stages, and to understand any time/environment-specific differences in microbiome composition over time. CSTs will be constructed using linkage clustering of microbiome species data. Given the repeated measurements for each participant and the longitudinal nature of this aim, the primary analytic method for continuous outcome measures will be linear mixed models. Normality assumptions will be accessed using normal probability plots. For binary outcomes, generalized estimating equations will be used. Covariates for all models will be HIV status, presence/absence of specific community states, vaginal PH, and demographic variables; covariates affecting the microbiome (e.g. CD4 count, ART exposure) will be included to assess their effect on treatment success rates. We will also use linear and generalized linear mixed models to detail the effects of individual microorganisms on CT treatment. Primary Outcomes: Association of CT treatment outcomes and BV-associated CSTs. *Findings from this sub-study could be clinically significant, as they may suggest that all pregnant women who are persistently positive for CT should be screened and treated for BV, even if they are asymptomatic.* Current evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women for the prevention of preterm birth.[156] Secondary Outcomes: 1) prevalence of BV in cases vs. controls based on Nugent score of 7-10 at first ANC visit, week 1 and 2, and 3 (ToC visit), and 2) Association of composition and structure of the vaginal microbiome over time at first ANC visit, week 1 and 2, and ToC in cases vs. controls at as a function of HIV viral load, CD4 count, and ART exposure. Exploratory Objectives: 1) Change in average relative abundance of indole-producing bacteria (i.e. *Prevotella* spp, *Fusobacterium nucleatum*, *Propionibacterium acnes, Porphyromonas gingivalis, E. coli*, and *Enterococcus faecalis)* over time in cases vs. controls, and 2) association of BV-associated CSTs with symptomatic or asymptomatic CT infection in cases vs. controls at first ANC visit.

Potential Limitations: Changes in the structure and composition of the vaginal microbiome can occur rapidly, at times within days.[157] As such, our currently proposed weekly sampling frame may limit our resolution to detect important changes. However, a recent prospective microbiome study in pregnant women found that vaginal community taxonomic composition and diversity remained remarkably stable during pregnancy.[143] Another limitation is our inability to exclude re-infection as the cause for a positive test result at ToC. Consequently, we will exclude or adjust our analysis based on self-reported high-risk sexual behavior between first ANC and ToC visits. To assess for re-infection, co-I Peters will perform CT genotyping on paired specimens of persistently positive participants using other existing funds.

Sample Size Calculations: Aim 1 analyses will explore intervention effects on reducing probabilities for adverse birth outcomes and STI prevalence at time of delivery. Based on a total sample size of ~2500 participants (~834 participants in each study arm), calculations show that we will have at least 80% power to detect study arm absolute differences of approximately 10% or larger in the frequency of adverse birth outcomes. We conducted two sets of calculations. 1) Calculations for the probability of an adverse birth event were conducted in PASS 2008 software (https://www.ncss.com/) for differences in proportions at a single time point (i.e., at birth). Calculations were run for a range of base rates ranging from 30% to 50%; this is in line with base rates from preliminary data (~40%). 2) We calculated changes in STI prevalence based on two time points (i.e., first ANC visit and birth) and conducted simulation studies in two steps. First, we simulated STI data from a binomial distribution with parameter values based on preliminary data. Preliminary results gave pregnancy STI rates around 40%; simulations used a range of pregnancy STI rates from 30% to 50%. Based on preliminary data, we anticipate that the intervention will reduce STI rates by 20% (absolute). We assumed an attrition rate of 15%.

Regarding aim 3, we assume 65 cases and 130 controls will provide four vaginal swabs allowing us to study the longitudinal association of vaginal microbiome characteristics and changes with persistent CT infection. Given the repeated observations within an individual, the non-independence of observations within a subject must be accounted for in the calculation. Assuming an intra-class correlation coefficient of 0.20, 200 women with 4 repeated observations provide 85% power to community state prevalence of 33% among non-responses as compared to 20% among responders using a two-tailed Type I error rate of 0.05. This effect size equates to a risk ratio of 1.65, an odds ratio of 1.97.

MULTIPLE PI LEADERSHIP PLAN

PI Klausner and PI Medina-Marino have collaborated together on infectious disease epidemiology and multiple intervention-based projects since 2010, when both were working together at CDC South Africa. They will share in the oversight of the entire project and the development, implementation and monitoring of all policies, procedures and processes. In these roles, PI Klausner and PI Medina-Marino will be responsible for the implementation of the scientific agenda and the specific aims, and ensure that systems are in place to guarantee institutional compliance with US and South African laws, DHHS and NIH policies including biosafety, human research activities, data collection and storage and facilities. Specifically, PI Klausner will oversee study design, methods, and clinical treatment protocols throughout the project, as well as oversight of US subcontracting partners as needed; he will make an in-person site visit to South Africa in each year of the project. PI Medina-Marino will be responsible for ensuring timely on-site implementation in South Africa, handling logistics, laboratory performance and ensuring community collaboration and communication with the study sites, government and non-government partners throughout the project. PI Klausner and PI Medina-Marino will jointly handle human subjects concerns and will jointly interpret and disseminate all study findings. All key decisions will be made by consensus whenever possible.

PI Klausner will serve as the contact PI and will assume fiscal and administrative management including maintaining communication among PIs and key personnel through regular weekly teleconference calls, e-mail communications, telephone calls. He will be responsible for communication with NIH and submission of annual reports. Publication authorship will be based on the relative scientific contributions of the PIs and key personnel.

Conflict Resolution

If a potential conflict develops, the PIs shall meet via telephone and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to an arbitration committee consisting of one impartial senior executive from each PI’s institution and a third impartial senior executive mutually agreed upon by both PIs. No members of the arbitration committee will be directly involved in the research grant or the disagreement.

CONSORTIUM/CONTRACTUAL AGREEMENT

Subaward Institution: Foundation for Professional Development (FPD)

Subaward PI: Andrew Medina-Marino, PhD

Project Period Dates of Sub: Years 1 - 5

Total Cost for Each Year:

Year 1: $664,010
Year 2: $849,378
Year 3: $837,232
Year 4: $694,110
Year 5: $358,530

SCOPE OF WORK

PI Medina-Marino will provide support for this study, led by PI Klausner at the University of California, Los Angeles (UCLA), from within the Foundation for Professional Development in South Africa.

FPD will house PI Medina-Marino, who will work with UCLA PI Klausner to oversee study design, methods, data analysis and dissemination efforts. Under Dr. Medina-Marino's leadership, the research team at FPD will oversee all field work and data collection, including contracts with laboratories at the University of Pretoria and University of Cape Town, which will manage microbiome processing and analysis in Aim 3. FPD will be responsible for completing all FPD administrative and IRB related requirements, ensuring timely on-site implementation in South Africa, handling logistics, and ensuring community collaboration and communication with government and non-government partners throughout the project. As this is a very large study taking place in South Africa, the field work portion of this study is substantial, and thus the majority of the project budget has been allocated to FPD.

UCLA will house Dr. Klausner, who will serve as contact PI for NIH. Under his leadership, UCLA will be responsible for completing all NIH and UCLA administrative and IRB-related requirements, overseeing the design, implementation and analysis of the study in coordination with Dr. Medina-Marino.

Though the role of FPD is significant for this project, it is appropriate for UCLA to be the grantee. UCLA and Dr. Klausner have extensive experience with NIH research projects and other major research grants of this nature. However, FPD's knowledge of the setting in which the research is taking place is integral to the project. The consortium agreement is appropriate, as Dr. Klausner will assume primary responsibility for the conceptualization, design, and analysis of the study while Dr. Medina-Marino and FPD staff will implement study activities in the international setting.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

CONSORTIUM/CONTRACTUAL AGREEMENTS

Subaward Institution: University of Alabama at Birmingham

Subaward PI: Christina Muzny, MD

Project Period Dates of Sub: Years 1 - 5

Total Cost for Each Year:

Year 1: $26,385
Year 2: $16,985
Year 3: $35,711
Year 4: $108,512
Year 5: $127,489

SCOPE OF WORK

Dr. Muzny will provide vaginal microbiome expertise and Dr. Redden will serve as senior biostatistician for this study, led by PI Klausner at UCLA and PI Medina-Marino at the Foundation for Professional Development, from within the University of Alabama at Birmingham (UAB).

While Drs. Muzny and Redden have an important role in this project, it is appropriate for UCLA to be the main grantee. UCLA has extensive experience with NIH research projects and other major research grants of this nature, including their existing partnerships with other subcontracting partners in this project, most notably with FPD. The consortium agreement is appropriate, as Dr. Muzny will provide guidance and support for the microbiome-related activities conducted in other laboratories and Dr. Redden will oversee the biostatistical analyses, while PI Klausner will oversee and coordinate the entire study along with PI Medina-Marino, including planning, implementation, analysis, and dissemination.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

CONSORTIUM/CONTRACTUAL AGREEMENTS

Subaward Institution: Louisiana State University

Subaward PI: Christopher Taylor, PhD

Project Period Dates of Sub: Years 1 - 5

Total Cost for Each Year:

Year 1: $14,280
Year 2: $14,280
Year 3: $14,280
Year 4: $55,038
Year 5: $50,883

SCOPE OF WORK

Dr. Taylor will provide vaginal microbiome expertise for this study, led by PI Klausner at UCLA and PI Medina-Marino at the Foundation for Professional Development, from within the Louisiana State University (LSU).

While Dr. Taylor and LSU have an important role in this project, it is appropriate for UCLA to be the main grantee. UCLA has extensive experience with NIH research projects and other major research grants of this nature, including their existing partnerships with other subcontracting partners in this project, most notably with FPD. The consortium agreement is appropriate, as Dr. Taylor will collaborate with UCLA on the analysis and visualization of the vaginal microbiome during years 4 and 5, and will provide consultation during years 1,2, and 3 on data collection and processing for the vaginal microbiome aim. During years 4 and 5, Dr. Taylor will utilize his computational resources, open source microbiome analysis software, and custom scripts and software developed in the Taylor lab for processing and analysis of the vaginal microbiome data. He will work with other investigators on data visualization and preparation of the manuscripts; meanwhile, PI Klausner will oversee and coordinate the entire study along with PI Medina-Marino, including planning, implementation, analysis, and dissemination.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

ANOVA HEALTH INSTITUTE

January 23, 2019

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Global Health
Division of Infectious Diseases and Program in Global Health
David Geffen School of Medicine and Fielding School of Public Health
University of California Los Angeles

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development (FPD)

Re: Letter of Commitment for NIH R01 submission

Dear Drs. Klausner and Medina-Marino:

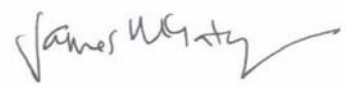
It is my pleasure to write this letter of commitment to serve as a scientific and clinical consultant for your proposed study **Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes**, to be funded by the NIH. I have thoroughly enjoyed, both personally and professionally, our collaboration over the past two years on your current NIH R21 study, *Pilot Study of STI Screening and Treatment for PMTCT*. It is always scientifically rewarding to see R21 funded exploratory work produce the type of exciting results that warrant submission of an R01. Yours has proven to be such a project.

I have spent more than 30 years as an OB-GYN physician-scientist, and working to eliminate mother-to-child transmission of HIV and improve the health of women and children worldwide. In my current role as executive director of the Anova Health Institute, my staff and I conduct research and provide technical assistance to national and local health departments in South Africa, Botswana, Malawi and Mozambique in order to improve health systems and delivery for people infected with or affected by HIV, STIs, and TB. I believe that your proposal to evaluate the impact and cost-effectiveness of different screening strategies to mitigate the burdens of untreated STIs on health outcomes of pregnant women and their babies is innovative and critically important. Your work may not only decrease the burden of STIs in your participants, their unborn children and communities but may also directly inform the outdated WHO guidelines relating to STI screening, especially during pregnancy. Furthermore, your aim to investigate the role of the vaginal microbiome in STI treatment failures and persistent infections is highly novel and innovative. Leveraging your intervention platform to also answer such cutting edge research questions will further the impact of your work.

For this study, I will provide support and advice as an OB-GYN and an expert in STIs, HIV, and Prevention-of-Mother-to-Child-Transmission of HIV. I will leverage my extensive experience conducting implementation science and public health research on the scale of that proposed here to ensure that your research study is a success. From my home in Johannesburg and my work throughout South Africa, I am in a strong position to lend critical thinking and logistical support to the implementation of this study and interpretation and contextualization of study findings. I will also continue to be a member of your Clinical Advisory Committee. I am able to commit an average of five hours of consultation per month, at the rate of $75 an hour, for a total of $4500.00 per year.

I am excited to continue collaborating with you both, and look forward to another fruitful scientific endeavor.

Sincerely,



Prof. James McIntyre, MBChB, FRCOG
Executive Director, Anova Health Institute
Honorary Professor, School of Public Health & Family Medicine, University of Cape Town

Dr Tracy L. Meiring
Division of Medical Virology
Institute of Infectious Diseases & Molecular Medicine
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January 3, 2019

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Public Health
University of California, Los Angeles
United States

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development
Pretoria, South Africa

Re: Letter of Commitment for NIH R01 Grant Proposal

Dear Drs. Klausner and Medina-Marino:

I am pleased to provide this letter of support for your research proposal ***Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes***, submitted as an NIH R01. As you are aware, I have served as a laboratory technical advisor on your recent NIH-funded STI project, during which we successfully built a very unique biorepository of self-collected vaginal specimens from a cohort of HIV-infected pregnant women for the analysis of the vaginal microbiome. We have also developed a strong collaboration and research infrastructure for the proposed research. As you know, to date, there have been no studies of the vaginal microbiome in South African pregnant women or HIV-infected pregnant women. The project will provide extremely important information on the vaginal microbiome and associations with STI treatment outcomes in pregnant women and future opportunities for research into the complex interplay between the vaginal microbiome, HIV and STIs during pregnancy and their potential impact on birth outcomes.

As an Early Research Career Fellow in the Division of Medical Virology and the Institute of Infectious Disease and Molecular Medicine at University of Cape Town (UCT), I look forward to being intimately involved in this study. As you know, I was among the first to use next generation sequencing to characterize human papillomaviruses (HPVs) in clinical specimens and I am currently carrying out a project examining the genital microbiome of South African women and men and associations of the microbiome with HPV infection. My experience and expertise in analysing the vaginal microbiome of South African women will allow me to contribute unique knowledge and context to this project.

For this project, I will provide expert scientific support and input with Drs. Muzny and Taylor in the analysis and interpretation of Aim 3 microbiome data. I will assist with protocol development, as well as training for microbiome specimen collection and handling in year 1. I will devote 10% level of effort (LOE) in year 1, 4 and 5. Given that my salary is fully covered by the South African National Research Foundation and UCT, I do not require any salary support for this project. In exchange for my time and LOE, I kindly request budget support for a fully-funded trip (i.e., conference registration, transport, accommodations and per diem) in years 1, 4 and 5 of the grant to attend relevant HIV/AIDS and STI conferences to assist in the dissemination of findings.

Given the excellent research environment and resources at UCT, together with your history of collaboration with me and others at UCT, I am confident that the proposed research will be carried out successfully. I look forward to working with you, Drs Muzny and Taylor, and the other members of your study team on this critical and innovative proposal.

Sincerely,

Tracy Meiring, PhD
Division of Medical Virology
Institute of Infectious Disease and Molecular Medicine
University of Cape Town
South Africa

ANOVA HEALTH INSTITUTE

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development (FPD)

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Global Health
Division of Infectious Diseases and Program in Global Health
David Geffen School of Medicine and Fielding School of Public Health
University of California Los Angeles

Re: Letter of Commitment for NIH R01 Grant Submission

Dear Drs. Klausner and Medina-Marino:

It is my pleasure to write this letter of commitment to serve as a scientific and clinical consultant for your proposed study ***Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes***, to be funded by the NIH. Our collaboration on your R21 pilot study of this same work has been quite rewarding to me, and I am very enthusiastic about seeing our work expand through this R01.

As you know, I am Head of Clinical Services at the Anova Health Institute, and affiliated professor at the Department of Microbiology at the University of Pretoria. In these capacities, I oversee both clinical work and laboratory work. In my recent collaboration with you, I was part of your Clinical Advisory Clinic, provided support and oversight for the collection of vaginal swab specimens to be bio-banked for future analysis, and shipping of specimens to collaborating laboratories at University of Cape Town. Furthermore, I also developed and oversaw proficiency testing of vaginal swab specimens, from which we co-authored a publication.

For this study, I will provide support and oversight of processing of laboratory specimens. I will leverage my laboratory infrastructure to conduct all Nugent scoring of vaginal specimens, specimen bio-banking, proficiency testing for study sights, and general support relating to specimen collection. Furthermore, I will also continue to be a member of your Clinical Advisory Committee, and will happily collaborate on data analysis and dissemination. For this work, I will only ask compensation for five hours of consultation per month, at the rate of $75 an hour, for a total of $4500.00 per year.

Given the strong history of collaboration between the Foundation for Professional Development, UCLA, and Anova Health Institute, I am certain that our research team will bring success to this proposed project. I look forward to again working with you and the other members of our team.

Sincerely,

Remco Peters, MD, PhD, DLSHTM
Anova Health Institute

904 Caribbean Drive
Sunnyvale, CA 94089
Telephone: (408) 541 4191
Facsimile: (408) 541 4192

January 11, 2019

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Public Health
University of California, Los Angeles
United States

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development
Pretoria, South Africa

Dear Drs. Klausner and Medina-Marino:

I enthusiastically write this letter of support for your study, "**Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes**," to examine the impact of different screening and treatment strategies on decreasing the burden of STIs among HIV-infected and uninfected pregnant women in South Africa.

Cepheid is dedicated to improving health and preventing the spread of STIs. Our GeneXpert® diagnostic platform is a rapid, PCR-based, point-of-care system that allows for the reliable and highly accurate detection of STIs in decentralized, community settings. Cepheid is happy to lend the required number of Xpert machines for the duration of your study at no cost. Finally, we will include training and technical support to your staff as needed, so they are able to use the equipment comfortably.

We thank you for the opportunity to continue to collaborate with you in this important work. We are confident this will be a fruitful partnership. Good luck with your proposal.

Sincerely,

David H. Persing, MD, PhD
Executive Vice President
Chief Medical and Technology Officer

School of Public Health and Family Medicine
Head of Department and Director: Professor Landon Myer

Division of Health Economics
Head: Associate Professor Edina Sinanovic

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E-mail: Edina.Sinanovic@uct.ac.za
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January 13, 2019

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Global Health
Division of Infectious Diseases and Program in Global Health
David Geffen School of Medicine and Fielding School of Public Health
University of California Los Angeles

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development (FPD)

Re: Letter of Commitment for NIH R01 Proposal

Dear Drs. Klausner and Medina-Marino:

It is with great enthusiasm that I write this letter in support of your proposed study, *Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes*. I am an associate professor in the Health Economics Unit and Division at the School of Public Health, University of Cape Town. I have significant experience and expertise as a health economist and health systems researcher, with particular interest in costs and cost-effectiveness of interventions to decrease the burden of HIV and STI. Undiagnosed and untreated STIs among pregnant women in South Africa, like in other countries, is a significant problem, as your current study of STIs in HIV-infected pregnant women shows. Consequently, your study to evaluate the cost and cost effectiveness of different diagnostic testing algorithms to decrease the burden of STIs during pregnancy and their impact on pregnancy and birth outcomes is of great potential benefit to public health and may inform future WHO recommendations.

As Co-Investigator, I will oversee all aspects related to the cost and cost-effectiveness component (Aim 2) of this grant proposal. In year 1 I will contribute 10% LOE, during which time I will develop all data-collection tools and oversee database development for the cost/cost-effectiveness components of the project. During years 2 and 3 (implementation phase), I will support and advise on data collection activities for Aim 2, and will contribute 5% LOE. Finally, in years 4 and 5, I will perform all data analysis and oversee all results dissemination emanating from Aim 2. This will require I contribute 45% and 55% LOEs in years 4 and 5, respectively.

Given the excellent resources available at UCT and the history of partnership between UCT and FPD, I believe our team will produce a well-executed study with critical impact on the field. I look forward to hearing the results of the Study Section's review.

Sincerely,

Susan Cleary, PhD
University of Cape Town

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YUNIBESITHI YA PRETORIA
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Enquiry: Prof Ute Feucht
Paediatrician, Head of Clinical Unit
ute.feucht@up.ac.za

Research Centre for Maternal, Fetal, Newborn & Child Health Care Strategies
Kalafong Hospital
Faculty of Health Sciences

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Date: 11 January 2019

Jeffrey D. Klausner, MD, MPH
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University of California Los Angeles

Andrew Medina-Marino, PhD
Head, Research Unit, Foundation for Professional Development (FPD)

Re: Letter of Commitment for NIH R01 Proposal

Dear Drs. Medina-Marino and Klausner:

As the Clinical Specialist Team Paediatrician for the Tshwane District Health Services and the University of Pretoria, it is my pleasure to write this letter of commitment to serve as a clinical consultant for your proposed study ***Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes***, to be funded by the NIH. I have had an excellent experience collaborating with you over the past two years on your current NIH R21 study, *Pilot Study of STI Screening and Treatment for PMTCT*. Given our collaboration, my expertise in maternal child health, I know first hand that your study to evaluate the impact of different screening and treatment strategies on decreasing the burden of STIs during pregnancy is a vital one, with the potential for huge impacts on our health district.

For this project, I will serve as a consultant Senior Technical Advisor. As you know I am a neonatal and infant health specialist, and an adjunct professor in the Department of Paediatrics and Child Health at the University of Pretoria. As I already do for your current R21 project, I will continue to serve on your study's Clinical Advisory Committee. From an implementation point of view, I will support and facilitate access to the antenatal care clinics in Tshwane District, where participant recruitment and STI testing will occur, and to maternal obstetric and paediatric units at local hospitals. From a research point of view, I will support data analysis and interpretation related to birth and neonate outcomes, and ensure ongoing support and dissemination of your findings within the leadership of Tshwane District Health Services.

For my time, I kindly request 5% level of effort salary support in years 1, 4 and 5, to be paid into a dedicated research fund at the Department of Paediatrics, Kalafong Hospital, University of Pretoria. Furthermore, I kindly request budget support for a fully-funded trip (i.e., conference registration, transport, accommodations and per diem) in years 2 and 3 of the grant to attend local HIV/AIDS, STI or maternal-child health conferences to assist in the dissemination of findings.

I am excited to continue collaborating with you both, and look forward to another fruitful scientific endeavor with a stellar research team.

Sincerely,

Dr. Ute Feucht
Adjunct Professor, Paediatrician, Head of Clinical Unit

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs, Research & Quality Assurance (AARQA)
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26.1.2019

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development (FPD)

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Global Health
Division of Infectious Diseases and Program in Global Health
David Geffen School of Medicine and Fielding School of Public Health
University of California Los Angeles

Re: Letter of Commitment for NIH R01 Grant Submission

Dear Drs. Medina-Marino and Klausner

It is my pleasure to submit this letter of support to demonstrate my commitment as a co-Investigator for your proposed NIH R01 grant entitled *Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes.* I have thoroughly enjoyed collaborating with Dr Medina-Marino since his time at CDC - South Africa, and look forward to collaborating with you both on this extremely important, timely and innovative research project.

I have spent more than 30 years as a medical microbiologist and have been actively involved in HIV Pathogenesis and Prevention research since 2003. I am currently the Executive Manager for Academic Affairs, Research and Quality Assurance (AARQA) at the National Health Laboratory Service (NHLS) and an honorary Associate Professor in the School of Laboratory Medicine and Medical Sciences at the University of KwaZulu-Natal (UKZN). In my AARQA Executive capacity, I oversee all the academic Pathology disciplines in the medical universities of the country, supporting research activities as well as teaching and training within pathology (undergraduate and postgraduate). As an honorary professor at UKZN, I continue with my research activities in tuberculosis as well as STI field. Our laboratory has established an STI diagnostic molecular platform and currently provides this service to research institutions like Centre for the Programme of AIDS Research in SA (CAPRISA) and another research unit at UCT.

I was the previously the Head of Department of the Medical Microbiology at UKZN responsible for overseeing provision of microbiological services to the province of KwaZulu Natal as well as the teaching of undergraduate and postgraduate students in Microbiology. Having been head of HIV Pathogenesis and Vaccine research at CAPRISA previously, I also was a coinvestigator and Project Director of the CAPRISA 004 tenofovir gel trial. I have extensive expertise in STIs and HIV; my PhD thesis was entitled "The Impact of Sexually Transmitted Infections (STI) and Genital Tract Inflammation on HIV-1 Acquisition and Rate of Disease Progression in Subtype C Infected Women." I therefore am highly familiar with the context of STIs in South Africa and was previously involved in the establishment of the STI syndromic management guidelines for the country in the mid-90s. Based on my experiences and insights, I can say that this study is very important to the field, innovative, and well-designed.

NATIONAL HEALTH LABORATORY SERVICE

For this project, I will serve as the co-Investigator providing expert support and oversight for 1) the implementation and operations of the GeneXpert diagnostic platform in all study clinics, 2) ensure access to and facilitate access to all laboratory test results from NHLS's laboratory information system, 3) facilitate process evaluations and costing data collection from key stakeholders within NHLS and NDoH. For this project, I will devote 10% level of effort (LOE). However, my salary is fully covered by the NHLS, as such I do not require any salary support for this project. In exchange for my time and LOE, I kindly request budget support for a fully-funded trip (i.e., conference registration, transport, accommodations and per diem) in years 1, 4 and 5 of the grant to attend relevant HIV/AIDS and STI conferences to assist in the dissemination of findings.

FPD frequently works closely with NHLS, and I know that your robust relationship with Cepheid and experience using the Gene Xpert in the field will make this a strong partnership. Ultimately, I look forward to working closely with you both on this project, and look forward to hearing the results of NIH review.

Kind regards

Prof Koleka Mlisana
Executive Manager: Academic Affairs, Research & Quality Assurance
MBChB, MMedPath(Micro), PhD

UAB SCHOOL OF MEDICINE
Department of Medicine
Division of Infectious Diseases

January 23, 2019

Andrew Madina-Marino, PhD
Foundation for Professional Development

Jeffrey Klausner, MD, MPH
UCLA

Dear Andrew and Jeff,

I am writing to assure you of my enthusiastic support and willingness to provide you with assistance in your NIH grant proposal entitled "Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes." With over 10 years of research experience in STIs and vaginal infections including the role of the vaginal microbiome in the pathogenesis of bacterial vaginosis (BV), I, along with my colleagues Christopher Taylor, PhD, and David Redden, PhD, are in excellent position to provide you and your research staff with expert guidance and feedback regarding the proposed study activities on the vaginal microbiome in Aim 3. Based upon my review of the specific aims that you have proposed, I believe the approaches you are taking will likely yield useful knowledge. Should any challenges arise with regards to the vaginal microbiome analysis, I have significant experience in troubleshooting alternative approaches and will be more than happy to do so for this proposal. I have enjoyed our collaborative research efforts to date and look forward to assisting you on this project. Good luck with your application.

Sincerely,

Christina Muzny, MD, MSPH

Christina Muzny, MD, MSPH
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Faculty of Health Sciences

SAMRC-UP MATERNAL AND INFANT HEALTH CARE STRATEGIES RESEARCH UNIT

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January 14, 2019

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Global Health
Division of Infectious Diseases and Program in Global Health
David Geffen School of Medicine and Fielding School of Public Health
University of California Los Angeles

Andrew Medina-Marino, PhD
Head, Research Unit
Foundation for Professional Development (FPD)

Re: Letter of Commitment, R01

Dear Drs. Klausner and Medina-Marino:

It is my pleasure to submit this letter of support to demonstrate my commitment to your proposed NIH R01 grant submission entitled Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes. As Professor and Clinical Head of the Department Obstetrics and Gynaecology, University of Pretoria, Chief Specialist at Kalafong Hospital, and Director of the South Africa Medical Research Council's (SA-MRC) Maternal and Infant Health Care Strategies Research Unit (MIHCSRU), I have more than 30 years of extensive expertise in maternal-infant health. Given this, I can say without hesitation, that this project is extremely important, timely and innovative. Over the past 7 years, I have worked closely with FPD on a number of projects, including our current collaboration to strengthen South Africa's public sector obstetric emergency medical systems services. I have enjoyed all of our collaborations, and look forward to working with you both on this currently proposed research project.

The SA-MRC MIHCSRU is co-located with Kalafong Hospital. Kalafong is one of the academic hospitals associated with the University of Pretoria, and is also one of this study's two maternal-obstetric units (MOUs). Kalafong has extensive research infrastructure and space to host large-scale research studies similar to what is being proposed in this R01 study. The MIHCSRU and Kalafong Hospital are two of Africa's leading centers for maternal-infant health research, with significant research funding and outputs; between 2011 and 2016, the MIHCSRU was awarded more than R113 million (~US$10 million),published more than 80 peer reviewed manuscripts, trained 13 PhD and Masters-level students and collaborated on 14 international research projects. Under my direction, the MIHCSRU regularly conducts research within the two hospital MOUs and catchment area ANC clinics proposed as study sites for this R01. Due to this relationship, staff at the MOUs and ANC clinics are well trained to complete

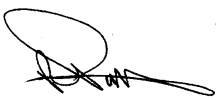
medical records and optimally collect factors related to birth outcomes. Ultimately, the selected study sites are outstanding locations in which to conduct this study.

For this project, I will serve as the Co-Investigator overseeing 1) the collection of specimens from mother-infant pairs admitted to hospital during and after delivery, and 2) the abstraction of medical records and discharge summaries for birth and pregnancy outcomes. Given that Kalafong Hospital is the main maternal-obstetric facility to which your study participants would be referred, I will ensure that vaginal specimens from the mothers and nasopharyngeal specimens from the neonates will be collected, and that all birth outcomes are properly recorded and reported. Additionally, as Director SA-MRC Maternal and Infant Health Care Strategies Research Unit, I have local and national networks of collaborators. I will leverage these networks and relationships, especially at Laudium Community Health Centre (the other local facility with a maternal-obstetric unit to which your study participants would give birth at) to ensure that they will provide the same type of access and support that I will provide at Kalafong Hospital. Our unit has had extensive experience with monitoring and following up pregnant women and their offspring. In one study we recruited 215 HIV infected women and followed these women throughout their pregnancies and the women and their babies for 3 years.

For this project, I will devote 10% level of effort (LOE). However, my salary is fully covered by the University of Pretoria, as such I do not require any salary support for this project. In exchange for my time and LOE, I kindly request budget support for a fully-funded trip (i.e., conference registration, transport, accommodations and per diem) in years 1, 4, and 5 of the grant to attend local AIDS, STI and maternal-infant health conferences to assist in the dissemination of findings. I also appreciate that you will provide 1) 100% LOE for a mid-wife research assistant in my unit starting in Q4 Year 1 through end of Year 3, and 2) 30% LOE for an administrative assistant for Y1 through Y3. The mid-wife research assistant will directly oversee all the post-delivery, in-hospital specimen collection and birth outcomes data collection for the project. The administrative assistant will provide programmatic support for any and all project specific activities occurring within my unit at Kalafong Hospital.

You have assembled an outstanding research team and I very much look forward to the important work that I will conduct with you on this project. I eagerly await the NIH review.

Sincerely,



Robert Pattinson, MBBCh, MMed, FCOG, MCCOG, MD
Director, Maternal and Infant Health Care Strategies Research Unit
South African Medical Research Council

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Enquiries: Prof Ute Feucht
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Jeffrey D. Klausner, MD, MPH
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University of California Los Angeles

Andrew Medina-Marino, PhD
Head, Research Unit, Foundation for Professional Development (FPD)

Re: Letter of Commitment for NIH R01 Proposal

Dear Drs. Medina-Marino and Klausner:

I am very excited to learn about your latest proposal to the NIH, called *Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes*, which is critical for the field. I am well aware that your previous work, *Pilot Study of STI Screening and Treatment for PMTCT in South Africa,* was also done in Tshwane District with our support and collaboration. Your findings have been well received, and your professionalism much appreciated. I am thankful for your continuous feedback sessions with district stakeholders, and for your respectful collaboration with your three study clinics; KT Motubatse clinic, Soshanguve CHC and Stanza Bopape CHC. It is my understanding that you adhered to all policies and requests made by facility managers, and that your staff integrated and worked well with facility staff. All this leads me to my willingness to continue supporting your research endeavours in collaboration with the district and our clinics.

Regarding your current proposed project, your effort to determine optimal diagnostic screening strategies to decrease the burden of STIs during pregnancy and on adverse birth outcomes is extremely important. Results showing that your interventions have impact will be necessary to reconsider health department guidelines and policy. However, your inclusion of a cost/cost-effectiveness component will be absolutely key to our ability to act on any recommendations. If proven to be impactful and cost effective, your work in Tshwane District may well have national, and perhaps international, consequences. We will be proud to say that your work was done in support of and in collaboration with Tshwane District Health Services.

I am fully aware that you both have substantial expertise as leaders in HIV and STD prevention and control research and program implementation, here in South Africa and internationally. Furthermore, the Foundation for Professional Development is one of our main partners supporting health-systems strengthening, thus you are known well within the district health system. As such, given this and our previous collaborations, I fully support the submission of your proposal and will happily work with you to continue this important work in Tshwane. This said, please note that this letter does not provide approval to conduct your research in Tshwane. Should you be awarded this grant, you will still be required to go through all appropriate process and procedures, including institutional review board approval from University of Pretoria, and district research committee approval before initiating your study.

I look forward to the sharing of study findings thereof. Best of luck on your application. If there's anything else I can do to support this work, please do not hesitate to contact me.

Sincerely,

Dr. Ute Feucht
Paediatrician, Tshwane District Clinical Specialist Team

World Health Organization

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28 January 2019

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University of California Los Angeles
10920 Wilshire Blvd, #350
Los Angeles, CA 90024

Dear Drs. Klausner and Medina-Marino,

RE: Clinical Study of STI screening to Prevent Adverse Birth and Newborn Outcomes

I was very pleased to learn about your new proposal to study the impact of screening and treating curable sexually transmitted infections (STIs) during pregnancy in South Africa.

As you know, the epidemiologic evidence shows that infection with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) during pregnancy may lead to various adverse birth and infant outcomes, including stillbirth, preterm delivery, low birth weight, congenital infection, and neonatal mortality. However, CT and NG infection in pregnancy have not been well-studied in South Africa. There are no national policies or programmes in place to screen pregnant women for those STIs. Furthermore, at the global level, the impact of antenatal CT/NG screening has not been adequately assessed. As a result, **there is no specific WHO recommendation for routine screening for CT and NG in pregnant women; the current standard of care is that pregnant women are not screened for these STIs.** Therefore, there is an urgent need for well-performed studies to demonstrate the benefits, risks, and costs associated with routine CT/NG testing and treatment during pregnancy.

The study you propose will address that need by providing valuable insight into the potential for routine antenatal screening to detect and treat previously missed cases of CT/NG. **We believe that such a study is critical to catalyzing local, national, and global policy change related to these important causes of adverse birth outcomes**. For example, your proposed research would provide critical information to aid in future guideline development for STI testing and treatment during pregnancy by the WHO. Most importantly, your research findings will contribute to improving health outcomes of mothers, neonates, and children in South Africa and in many other countries.

I would like to express our strong support for your proposed study on CT and NG in pregnancy.

Yours sincerely,

Dr Teodora Wi
Medical Officer STIs
Department of Reproductive Health and Research (RHR)
Human Reproduction (HRX)

RESOURCE SHARING PLAN

Data Sharing

In order to support the free flow of information and ideas to improve scientific research, the project team is solidly committed to regular sharing of data collected through this study. All study data will be kept in electronic databases, with access provided to all key staff. Programming codes will be available to any investigators who request such data directly from the Project PIs. All data will be provided on CD and will be completely de-identified. A data sharing agreement must be completed and signed by the requesting investigator and representatives of FPD, UCLA, the University of Alabama at Birmingham, Louisiana State University, and/or the University of Cape Town (as applicable) before this transfer of data can be made. Datasets will be available outside the core study team at a minimum once the data have been accepted for peer-reviewed publication, and earlier if the data are deemed by the PIs to be clean and the sharing of data is not expected to inhibit future opportunities for publication.

AUTHENTICATION OF KEY BIOLOGICAL/CHEMICAL RESOURCES

Key Biological Resources. There will be no non-standardized biological agents used in Aim 3. Mock community bacterial collection used as a sequencing control in Aim 3 will be obtained from BEI (USA) (https://www.beiresources.org/Catalog/otherProducts/HM-782D.aspx) strain collections, which ship authentication documents with the bacteria. Mock community samples will be analyzed after each sequencing run to ensure the detected species of bacteria are those present in the mock community. In case of any significant deviation from the mock community specification, new aliquots will be ordered from BEI prior to the next sequencing run.

Other Novel Reagents. Only qualified commercial vendors that comply with quality standards will be considered as suppliers. The biological reagents and sequencing reagent kits will be purchased from QIAGEN and Illumina, companies that comply with good manufacturing practice standards fulfilling the requirements of *in vitro* diagnostics. Each purchase is supplied with a quality control data sheet. Regents will be stored at -20ºC according to manufacturer specification to avoid degradation after receipt and prior to use in experiments.

PHS Assignment Request Form

Funding Opportunity Number: PA-19-055

Funding Opportunity Title: Research Project Grant (Parent R01 Clinical Trial Required)

Awarding Component Assignment Request *(optional)*

If you have a preference for an awarding component (e.g., NIH Institute/Center) assignment, use the link below to identify the appropriate short abbreviation and enter it below. All requests will be considered; however, assignment requests cannot always be honored.

Awarding Components: https://grants.nih.gov/grants/phs_assignment_information.htm#AwardingComponents

	First Choice	Second Choice	Third Choice
Assign to Awarding Component:	NIAID		
Do Not Assign to Awarding Component:			

Study Section Assignment Request *(optional)*

If you have a preference for study section assignment, use the link below to identify the appropriate study section (e.g., NIH Scientific Review Group or Special Emphasis Panel) and enter it below. Remove all hyphens, parentheses, and spaces. All requests will be considered; however, assignment requests cannot always be honored.

Study Sections: https://grants.nih.gov/grants/phs_assignment_information.htm#StudySection

	First Choice	Second Choice	Third Choice
Assign to Study Section: *(only 20 characters allowed)*	CRFS		
Do Not Assign to Study Section: *(only 20 characters allowed)*			

PHS Assignment Request Form

List individuals who should not review your application and why *(optional)* *Only 1000 characters allowed*

Identify scientific areas of expertise needed to review your applications *(optional)*

Note: Please do not provide names of individuals

	1	2	3	4	5
Expertise: *Only 40 characters allowed*	STI	Microbiology	Cost-effectiveness analysis	HIV	Maternal-Fetal Medicine

PHS Human Subjects and Clinical Trials Information

Are Human Subjects Involved	●Yes		❍No					
Is the Project Exempt from Federal regulations?	❍Yes		●No					
Exemption Number	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8
Other Requested Information								

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes	Yes

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

Section 1 - Basic Information (Study 1)

1.1. Study Title *

Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes

1.2. Is this study exempt from Federal Regulations? * ❍Yes ●No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	●Yes	❍No
1.4.b. Are the participants prospectively assigned to an intervention?	●Yes	❍No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	●Yes	❍No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	●Yes	❍No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics

2.1. Conditions or Focus of Study

- Pregnant women in South Africa
- Neonates born to study participants

2.2. Eligibility Criteria

Pregnant Women: 1) Age 18 years and older, 2) Currently pregnant, 3) Attending first ANC visit for their current pregnancy, 4) Willingness to self-collect up to four vulvo-vaginal swabs, 5) Residence in Tshwane District, and 6) Intent to stay in Tshwane District through delivery

Neonates: 1) born to mothers that provided informed consent to participate in study, 2) provision of updated verbal consent by mother to collect and test specimens for STIs

2.3. Age Limits	Min Age: 0 Years Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	Women__Minorities__Children1054050514.pdf
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Plan1054050517.pdf
2.6. Recruitment Status	Not yet recruiting
2.7. Study Timeline	Study_Timeline1054050516.pdf
2.8. Enrollment of First Subject	09/01/2019 Anticipated

Inclusion Enrollment Reports

Entry#	Enrollment Location Type	Enrollment Location
IER 1	Foreign	Three large antenatal care clinics in Tshwane District, South Africa

Section 3 - Protection and Monitoring Plans

3.1. Protection of Human Subjects

Protection_of_Human_Subjects1054050512.pdf

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? ❍ Yes ● No ❍ N/A

If yes, describe the single IRB plan

3.3. Data and Safety Monitoring Plan

DSMP_rev1054114385.pdf

3.4. Will a Data and Safety Monitoring Board be appointed for this study? ● Yes ❍ No

3.5. Overall Structure of the Study Team

Study_Team1054050510.pdf

Section 4 - Protocol Synopsis

4.1. Brief Summary

In 2012, WHO estimated that over 350 million cases of Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG) and Trichomonas vaginalis (TV) occurred globally. Sexually transmitted infections (STIs) during pregnancy are associated with premature rupture of membranes, preterm labor and delivery, low birth weight, congenital infections, perinatal death and mother-to-child transmission of HIV infection.

STIs are common in pregnant women globally, but often go undiagnosed; recent work by our group found a 41% STI prevalence amongst HIV-infected pregnant women, of which 64% of infections were asymptomatic. Recent research suggests the vaginal microbiome may play a critical role in STI acquisition, persistence and treatment outcomes. Our pilot work has shown that diagnostic testing for CT, NG, and TV in antenatal care services for HIV-infected pregnant women in South Africa is highly acceptable and feasible; however, our work has made clear that evaluating the impact and cost effectiveness of different diagnostic screening strategies that optimally decrease the burden of STIs during pregnancy and at time-of-delivery is urgently needed. Furthermore, our findings highlight that biological factors that increase the risk for STI persistence and/or treatment failures must be further investigated.

In response to the need to 1) identify cost effective screening strategies that optimally decrease the burden of STIs during pregnancy, and reduce adverse pregnancy and infant outcomes, 2) elucidate the role of the vaginal microbiome in treatment outcomes, and 3) inform STI screening and treatment guidelines in other low-middle income countries, we propose a novel, highly innovative study with the following three Aims:

Aim 1: Evaluate different screening strategies to decrease the burden of CT/NG/TV among pregnant women, and reduce adverse birth outcomes.

Aim 2: Evaluate cost per pregnant woman screened and treated, cost of adverse birth outcomes, and cost-effectiveness per STI and disability-adjusted life year (DALY) averted.

Aim 3: Investigate the relationship between the vaginal microbiome and persistent Chlamydial infections in pregnant women.

Our proposed 5-year study will enroll 1250 HIV-infected and 1250 uninfected pregnant women from three large ANC clinics in Tshwane District, South Africa, as well as their neonates. Our research team, led by established researchers, has significant expertise and experience in all aspects of the proposed study. Our multi-institutional collaborations will allow us to leverage unique implementation platforms and resources, and allow for rapid dissemination of findings to South African and global stakeholders.

4.2. Study Design

4.2.a. Narrative Study Description

This effectiveness trial will increase understanding of the value and cost-effectiveness of diagnostic screening for sexually transmitted infections (STIs) among pregnant women in low and middle-income countries, to reduce adverse pregnancy and infant outcomes. Further, results from this study will provide important data on the role of the vaginal microbiome in Chlamydia trachomatis (CT) testing outcomes and further rationale for studying the vaginal microbiome in pregnant women with CT treatment failure. Together, findings from this R01 are likely to inform changes to STI screening and treatment guidelines in low-middle income countries globally.

4.2.b. Primary Purpose: Screening

4.2.c. Interventions

Type	Name	Description
Diagnostic Test	Single point-in-time molecular diagnostic screening for CT, NG and TV and follow-up test of cure	Pregnant women will be screened for CT, NG, and TV during their first ANC visit. Those who test positive for any of the three infections will be given targeted treatment and asked to return for follow-up test-of-cure (ToC) three weeks post-treatment. Repeat ToC will be performed and treatment provided until a negative ToC or birth outcome is recorded.
Diagnostic Test	Periodic molecular diagnostic screening for CT, NG and TV	Pregnant women will be screened for CT, NG, and TV during their first ANC visit and again 30-34 weeks gestation. Those who test positive for any of the three infections at any one of the two screening time-points will be be given targeted treatment but will not undergo test-of-cure.

4.2.d. Study Phase: Phase 3

Is this an NIH-defined Phase III Clinical Trial? ● Yes ❍ No

4.2.e. Intervention Model: Parallel

4.2.f. Masking: ❍ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation: Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	Frequency of adverse birth outcomes per study arm	End of Pregnancy	This the number and proportion of women who have a miscarriage, still-birth, experience preterm-premature rupture of membrane, preterm delivery or delivery to a low birth-weight baby. This outcome will be compared between the different study arms.
Secondary	Incident infections identified at time of birth outcome, by study arm	Duration of pregnancy, from 1st ANC visit to end of pregnancy/delivery	This outcome is the proportion of women who test positive for CT, NG, and/or TV shortly after delivery among women who tested negative for those three infections at the first ANC visit or during a test-of-cure visit.
Secondary	Incidence of CT, NG, and/or TV colonization among neonates	First week of life	Neonates born to mothers who test positive for CT, NG, and/or TV shortly after delivery will tested to determine what proportion are colonized with the same organism as the maternal infection.

4.4. Statistical Design and Power: Statistical_Design_and_Power1054050515.pdf

4.5. Subject Participation Duration: Participants with miscarriages or stillbirths remain in the study until their first clinic visit after their pregnancy outcomes. Those who deliver live babies will remain in the study until the baby's sixth month of life.

4.6. Will the study use an FDA-regulated intervention? ● Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status: IDE_Status1054050511.pdf

4.7. Dissemination Plan: Dissemination_Plan1054050513.pdf

Section 5 - Other Clinical Trial-related Attachments

5.1. Other Clinical Trial-related Attachments

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ❍Yes ●No

Enrollment Location Type* : ❍Domestic ●Foreign

Enrollment Country(ies): ZAF: SOUTH AFRICA

Enrollment Location(s): Three large antenatal care clinics in Tshwane District, South Africa

Comments: Planned participants include 2500 pregnant women, ~2500 neonates born to them (estimated gender breakdown of 50% male, 50% female), and up to 834 male partners of pregnant women who are expected to test STI positive in Arms 1 and 2 (n=667) or be identified via one-time diagnostic screening in Arm 3 (n=167). We will also interview ~20 research, clinic, and admin staff in Aim 2 (gender breakdown of 65% female and 35% male, per typical gender breakdown in South African healthcare settings).

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3763	2091	0	0	5854
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	3763	2091	0	0	5854

Cumulative (Actual)

Racial Categories	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			Total
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native										0
Asian										0
Native Hawaiian or Other Pacific Islander										0
Black or African American										0
White										0
More than One Race										0
Unknown or Not Reported										0
Total	0	0	0	0	0	0	0	0	0	0

INCLUSION OF WOMEN AND MINORITIES

100% of participants in this study will be pregnant South African women, which is appropriate given the study focus and aims. Therefore all participants will be women. Given the demographics of the clinical catchment area populations, we expect that all participants will be minorities (Black Africans).

INCLUSION OF CHILDREN

Neonates born to study participants will be included in this study. As per South African law, maternal/parental consent for inclusion and testing of neonates/infants will be sought. Nasopharyngeal swab specimens will be collected from neonates/infants and data will be abstracted from their medical records. Study staff have extensive experience with neonatal patients within the antenatal care settings of this study.

RECRUITMENT AND RETENTION PLAN

All participant recruitment will occur in one of three ANC clinics in Tshwane District South Africa. Study staff will be trained in the study's methods, protocol, and human subjects research, and will conduct eligibility screening on all patients attending their first ANC visit, following a simple, standard checklist of eligibility criteria. Staff will read all eligible women a brief description of the study. Interested women will then be read aloud the study consent form in their preferred language, which will provide specific information about CT, NG and TV infections, the consequences and treatment of those infections, and study risks and benefits, and then will be invited to participate in the study. Staff will collect basic de-identified information from clinic logs (i.e., age, cultural group, gestational age, HIV status) to use for descriptive analysis of the general ANC patient population.

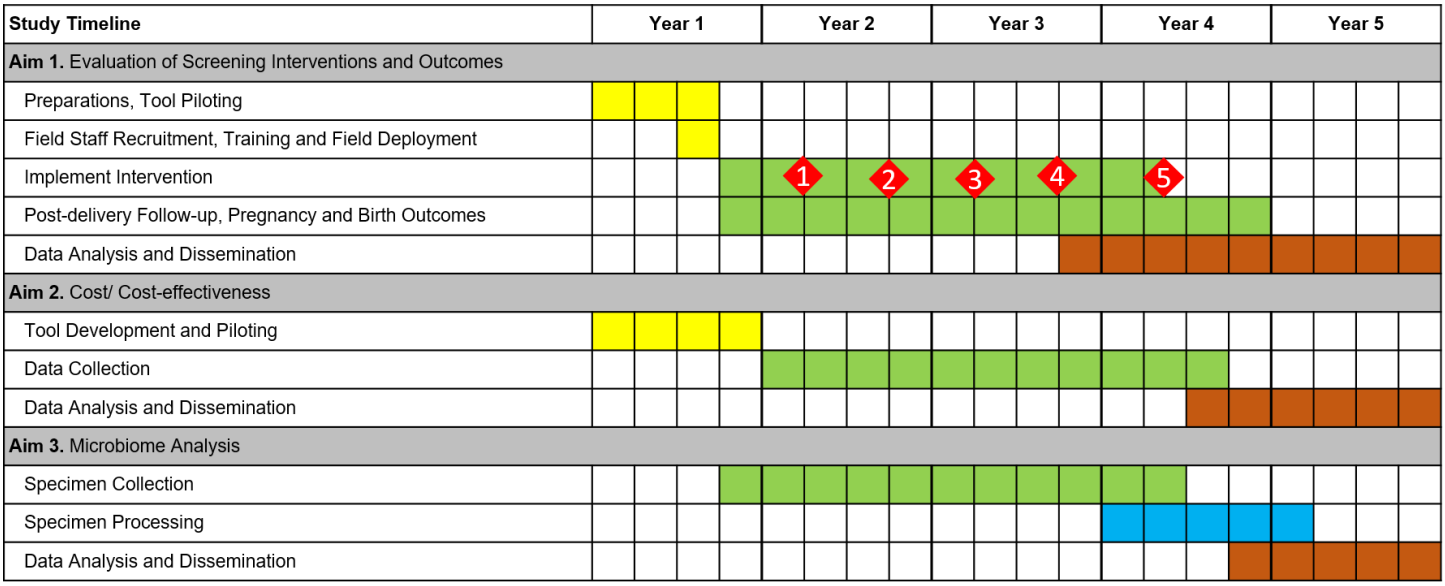
To ensure retention, those providing informed consent will be asked to provide detailed contact information (e.g., phone numbers and "home address" for self, family, friend/neighbor) to ensure follow-up. To develop and maintain a strong relationship with participants, study staff will conduct welcome phone calls within 3 days of enrollment, and check in with participants during regular ANC clinic visits, or during monthly ART pickup for those with HIV infections. To further support active follow up, participants will also be encouraged to enroll in the UNICEF-funded MomConnect program, which sends reminder messages to pregnant women's mobile phones via text messages to remind them about their upcoming ANC visits, and automatically generates alerts for clinic staff when appointments are missed. Clinic and study staff will contact participants who do not return for scheduled ANC or ART visits and encourage return for care.

We will flag participant charts so that clinic staff will notify study staff on the date of delivery. Seven days post-delivery, study staff will contact participants that have not yet presented for their first postnatal clinic visit to schedule an outcomes interview. We will make up to 7 attempts to follow up with participants via text, phone call, and home visits. At the outcome interview, we will collect data on adverse pregnancy events; at this time we will also seek updated verbal consent by the mother to collect and test specimens for STIs from their neonate (as previously consented at the time of enrollment).

STUDY TIMELINE

This study encompasses four major phases, as color highlighted in the table below.

- Phase 1 (yellow): Protocol development, IRB submission; Develop and pilot clinical and costing data collection tools; Develop participant, specimen and implementation tracking tools; Staff hiring and training; Deploy staff to the field
- Phase 2 (green): Participant recruitment, testing, treatment, ToC and follow-up; Microbiome specimen collection; Clinical and costing data collection; Postnatal follow-up, testing and outcomes data collection; Data cleaning and management
- Phase 3 (blue): Specimen selection for Nugent scoring and vaginal microbiota analysis; Microbiome specimen processing and sequencing
- Phase 4 (brown): Data analysis, dissemination of findings, and preparation for future research.



- Additive Recruitment Milestones (red diamonds):
  - Milestone 1: 300 participants
  - Milestone 2: 400 participants
  - Milestone 3: 500 participants
  - Milestone 4: 500 participants
  - Milestone 5: 800 participants

- Cumulative Recruitment Milestones (red diamonds):
  - Milestone 1: 300 total participants
  - Milestone 2: 700 total participants
  - Milestone 3: 1200 total participants
  - Milestone 4: 1700 total participants
  - Milestone 5: 2500 total participants

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design

For Aim 1, All pregnant women attending their first ANC visit at one of the participating clinics will be screened for eligibility by study staff following standard HIV testing per South African National Guidelines for the prevention of mother-to-child transmission of HIV. Those providing informed consent will be enrolled and within each clinic randomized (1:1:1) into one of the 3 study arms using a simple random allocation list created in Microsoft Excel before the initiation of recruitment activities; each study arm will be composed of 50% HIV-infected (purposive enrichment) and 50% HIV-uninfected women. **Arm 1)** single point-in-time molecular diagnostic screening for CT, NG and TV with targeted treatment at first ANC visit and infection-specific ToC 3 weeks post-treatment. Women with a positive ToC will be re-treated and requested to return every 3 weeks for follow-up ToC visits until a negative ToC or birth outcome is documented. **Arm 2)** periodic molecular diagnostic screening for CT, NG and TV at first ANC visit and week 30–34 gestation with targeted treatment. No ToC will be conducted for women with positive test results. **Arm 3)** one-time diagnostic screening at first ANC visit, with targeted treatment but no follow-up ToC or repeat testing.

Consenting participants will be instructed on how to self-collect a vulvo-vaginal swab specimen and asked to provide up to four swabs: 2x swabs for STI testing, 1x swab for microbiome analysis, 1x swab for bio-banking (NOTE: our recent study has demonstrated that pregnant women found it acceptable and feasible to collect up to four vaginal swabs at a visit). If a participant is not comfortable with self-collecting a vulvo-vaginal swab specimen they will be given the option to provide a urine specimen for testing and bio-banking. Vaginal specimens collected from participants will be PCR-tested for CT, NG and TV using the Xpert® CT/NG and Xpert® TV cartridges [Cepheid, Sunnyvale, CA]. Study nurses will be responsible for providing same-day test results notification and immediate treatment (and partner treatment) to all STI-infected study participants per the South African Department of Health's STI treatment protocols.

Regardless of the Arm to which they are randomized, all study participants will also be asked to provide four vaginal swab specimens during their first postnatal clinic visit (typically 3-6 days after discharge) or at the earliest time possible after they give birth. Reporting of test results and provision of treatment for those with a positive test result will be conducted as described above. Two nasopharyngeal (NP) swab specimens will also be collected from all infants during the first postnatal visit. For any woman with a post-partum prevalent STI, staff will test the infant's nasopharyngeal swab at that visit for that same infection (CT, NG and/or TV) to exclude mother-to-child transmission. If no maternal infections are identified, both nasopharyngeal swabs will be bio-banked. Any neonate who has an NP specimen positive for CT, NG and/or TV will be treated according to treatment recommended in the South African Medical Formulary.

For Aim 2, no human subjects will be involved.

For Aim 3, participants randomized to Arm 1 in Aim 1 and who test positive for a CT mono-infection during their first ANC clinic visit will be invited to participate in the Aim 3 CT sub-study: a weekly vaginal specimen collection activity until a negative ToC result or a birth outcome is documented. At week 1, week 2 and the Test of Cure (ToC) visit (week 3), participants will be asked to collect vaginal swabs as described in Aim 1. At ToC (week 3), participants will be repeat CT-tested. Those with a positive CT test result at ToC will again be treated with azithromycin 1 gm by directly observed therapy, and asked to return for subsequent weekly specimen collection (weeks 4 and 5) and ToC2 (week 6), to be collected as previously described.

In total, 2500 participants enrolled in the study will be pregnant women; with the mother's consent at the time of enrollment, approximately 2500 neonates (estimated 1 per adult participant) will also be enrolled upon birth.

Collaborating sites where human subjects research will be performed: Specimen collection and STI testing using the Gene Xpert will be performed on-site at each of the participating ANC clinics in Tshwane district. Specimens will be transported to the Department of Medical Microbiology, University of Pretoria, on a bi-weekly basis, where they will then be flash frozen and stored for long-term bio-banking. Specimens will be processed at the University of Cape Town for microbiome analysis.

Study Procedures, Materials, and Potential Risks

Planned Research Procedures and Materials: In additional to vaginal specimens collected as described above, trained study staff will administer an ACASI-based questionnaire to all pregnant female participants. The ACASI questionnaire will include: 1) participant demographics and socio-economic status, 2) obstetric, gynecological and sexual health history, 3) sexual behaviors, risk factors and self-perception of risk for HIV and STI acquisition before and during pregnancy, 3) partner characteristics and HIV status, 4) knowledge and previous history of STIs, and 8) screenings for depression, substance abuse, interpersonal violence and social support. Staff will translate ACASI questionnaires into the major local languages (i.e., English, Sepedi, Setswana, Zulu, and Ndebele). Participants may select their preferred language in which to take the ACASI questionnaire, but will also be able to toggle between languages during the questionnaire to ensure linguistic comprehension of all questions. Staff will abstract from clinical records additional clinical history, including HIV status, date of diagnosis, and immunological characteristics associated with HIV infection (e.g., CD4 T-cell level, HIV viral load, antiretroviral therapy (ART) use and duration). Staff will verify self-reported and medical record-abstracted HIV-related information with data from the South African national HIV database, Tier.net, and the South African National Health Laboratory Service (NHLS) corporate data warehouse, both of which contain individual heath data. For neonates, two nasopharyngeal (NP) swab specimens will be collected during the first postnatal visit. For any woman with a post-partum prevalent STI, staff will test the infant's nasopharyngeal swab at that visit for that same infection (CT, NG and/or TV) to exclude mother-to-child transmission. If no maternal infections are identified, both nasopharyngeal swabs will be bio-banked. Any neonate who has an NP specimen positive for CT, NG and/or TV will be treated according to treatment recommended in the South African Medical Formulary. HIV PCR results from routine at-birth testing of HIV-exposed infants will be collected via clinical records, and verified using the NHLS database. At the routine 6-week immunization visit, we will access neonatal morbidities (i.e., respiratory distress, conjunctivitis, sepsis) via maternal interviews and patient medical records.

Linkages to subjects and access to subject identities: All study participants will be assigned a unique participant ID that does not include personally identifying information such as initials or date of birth. All identifiable contact information will only be accessible by study staff who need it in the course of their work, and will be kept in a locked cabinet, unlinked and in a separate location from all participant IDs at all times, with the linking key only available to one key staff member of the team to protect confidentiality.

Potential Risks to Participants: The primary potential risks to participants due to study participation are psychological and social in nature. Physical risks from vaginal or nasopharyngeal swab collection (i.e., mild discomfort) are negligible.

- *Psychological:* Participants could experience psychological distress such as anxiety when discussing issues related to personal experiences, sexual health, or pregnancy. However, we do not expect any serious events to occur based on our experience across multiple previous studies, including our pilot study with this same population in South Africa. Participants may experience some stress related to the knowledge of STI or HIV status. Participants will be given information and education about the nature and consequences of all infections and treatment, and those testing positive (including newborns) will be provided treatment as per standard treatment protocols. The likely harmful consequences of learning one's STI status are low.

- *Social:* Participation in this study may cause social harm (e.g., discrimination, false assumptions, rumors) if the participation of the participant becomes known to others. One of the more significant risks is notification of sexual partners about positive results of CT, NG, or TV testing, which is an important step to protect the health of the partners and their future contacts. It is possible that notifying partners about a positive CT, NG, or TV test could put the participant at risk for intimate partner violence (IPV). Given this, we will provide IPV prevention counseling and will take steps to mitigate and monitor such outcomes, providing intensive participant support as needed.

Alternative treatments and procedures: Participants from the target population invited to participate will be able to decline participation, with no consequence to them.

Adequacy of Protection Against Risks

Informed Consent and Assent

Staff will read all eligible women a brief description of the study. Interested women will then be read aloud the IRB-approved study consent form in their preferred language, which will provide specific information about CT, NG and TV infections, the consequences and treatment of those infections, and study risks and benefits, and then will be invited to participate in the study. At the outcome interview post-birth, we will seek updated verbal consent by the mother to collect and test specimens for STIs from their neonate (as previously consented at the time of enrollment). More information about recruitment and informed consent is available in the Recruitment and Retention Plan.

Protections Against Risk

The risk of loss of privacy will be controlled using standard data collection protocols, trained staff with regular supervision and unique participant ID numbers on all data (including specimens) rather than participant names. Research staff will take an oath of confidentiality. Psychological stress will be reduced for STI testing through information and education and the use of trained staff, who will have experience in mitigating IPV. Participants who wish to disclose their test results to key individuals in their life will be offered help and counseling to do so, including an information sheet for significant others which has been developed by FPD for their current PrEP R01 study, and will be adapted for this study. For women reporting IPV upon disclosure to their partners, appropriate counseling, care and referral will be offered. Furthermore, a toll-free telephone/text hotline will be set up for all participants that encounter such social harms to receive support and/or advice.

Potential Benefits of the Proposed Research to Research Participants and Others

The potential benefits to subjects include receiving basic information about STIs and HIV, as well as learning their CT, NG, and TV status and receiving treatment when indicated, which could have positive effect on their health and the health of their baby. Neonates who are diagnosed with CT, NG, or TV will benefit from early treatment for these infections.

Importance of the Knowledge to be Gained

Findings from this study have the potential to substantially affect STI screening and treatment guidelines for pregnant women in low and middle-income countries, to decrease the burden of STIs during pregnant and reduce adverse pregnancy and infant outcomes as a result of undiagnosed STIs. The minimal risks to subjects in this study are reasonable in relation to the important knowledge to be gained about the impact of STIs on adverse birth outcomes, and potential for widespread changes to national STI screening policies for pregnant women as a result.

DATA, SAFETY, CLINICAL MONITORING PLAN

OVERSIGHT RESPONSIBILITIES
Oversight of the trial is provided by the Principal Investigators (PIs), Dr. Medina-Marino and Dr. Klausner, throughout. A detailed Data and Safety Monitoring Plan will be submitted to the University of Pretoria and UCLA IRBs and approved by the NIH prior to the accrual of human subjects.

MONITORING PROCEDURES
Dr. Medina-Marino will ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for Drs. Medina-Marino and Klausner to review. The PIs will review study conduct (including enrollment, drop-outs or loss to follow-up, and protocol deviations) on a bi-monthly basis. The PIs and co-Investigators will review, in real-time and in aggregate on a monthly basis, any Adverse Events (AEs) or Adverse Birth Outcomes (ABOs) that occur. Due to the low-risk nature of this intervention trial, however, we expect few to no AEs to occur. The PIs will ensure all protocol deviations, AEs, and SAEs are reported to the NIH, University of Pretoria, and UCLA IRBs according to the applicable regulatory requirements.

ESTABLISHMENT OF A DATA AND SAFETY MONITORING BOARD
The monitoring responsibilities of the PIs will be augmented by an external Data and Safety Monitoring Board (DSMB) convened for the purpose of this study.

The DSMB will be an independent group of experts made up of five, non-study associated national and international experts, including a biostatistician and OB/GYN clinicians knowledgeable about STIs during pregnancy and adverse birth/pregnancy outcomes. The DSMB will be charged with reviewing data quality and scientific integrity, adherence to the protocol, participant safety, study conduct and progress, and making determinations regarding study continuations, modifications, and suspensions/terminations. ***Given the high rate of asymptomatic infections and the concerns regarding syndromic management (standard of care arm), the DSMB will also be specifically charged to assess for early evidence of harm or benefit.***

DSMB members will be independent from any professional or financial conflict of interest (COI) with the research project and/or study investigators. The PIs will provide the names of potential DSMB members to NIH for review and approval, along with their qualifications and a COI statement indicating that the proposed members have no direct involvement with the study or COI with the investigators conducting the study. When ascertaining independence, DSMB members may be affiliated with the investigator's institution or other participating sites, but will not be a scientific collaborator or co-author, supervisor, mentor/mentee, subordinate of the investigators, or a member of the investigator's institutional department within the last three years.

The DSMB will review in aggregate on a quarterly (3 month) basis any AEs, including social harm or abnormal laboratory/test result, or ABOs, regardless of whether they are considered related to study exposure. Occurrence of AEs will be captured during study visits, or during routine follow-up communications with participants outside of clinic-based appointments. ABOs will recorded within 7 days of event. Regularly performed interim analyses will be conducted to monitor for AEs and ABOs associated with study arms.

COLLECTION AND REPORTING OF SAEs AND AEs
For this study, the following standard AE definitions will be used:

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs will be graded according to the following scale:

Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study will use the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

AEs will be identified through participant self-report, by clinician or project staff report, or during follow-up survey periods as described in the study methods.

SAEs and specific procedure-associated AEs will be reported, in writing and with a follow-up phone call by Dr. Medina-Marino to the NIH and University of Pretoria IRB within 24 hours after an AE or SAE is identified; Dr. Klausner will notify the UCLA IRB as proposed. In addition, all AEs are reported according to the University of Pretoria and UCLA IRB's AE reporting guidelines.

PLAN FOR ASSURING DATA ACCURACY AND PROTOCOL COMPLIANCE

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process, which includes monthly review of collected data by the UCLA Research Assistant, and quarterly review of collected data by the PIs.

NLM REPORTING OF CLINICAL TRIAL FINDINGS

The clinical trial will be pre-registered on ClinicalTrials.gov, and all findings produced via that pre-registered protocol will be reported according to the requirements of CONSORT 2010.

INDEPENDENT CLINICAL MONITORING

An independent study monitor will be hired to ensure the proper conduct of the study. A monitoring plan will be developed prior to study initiation. During the course of the study, a qualified independent, external study monitor will regularly review study data and informed consent. The monitor will make site visits as needed and as feasible, but a minimum of one initiation training visit, one interim monitoring visit per year, and one close-out visit to assure that the study is being conducted and informed consent is being obtained according to the approved protocol, and to monitor recruitment and data accuracy.

The site Principal Investigator (Medina-Marino) or designee will securely maintain all source documents used to complete CRFs, including medical chart notes, laboratory reports, and documentation of referrals. The site may be asked to send copies of some source documentation, with participant identifiers expunged, to the Data Monitoring and Safety Board. They may also send administrative documentation to the DSMB for review. While some CRFs may serve as source documents, all documents or records that will serve as source documentation for this study will be fully outlined in the study manual. All study records will be retained unless an exception is granted.

Investigators and study staff will allow the study monitor and other authorized DSMB members, health regulatory agencies staff and other relevant personnel to inspect files, study documents (e.g., consent forms, case report forms, other source documents) and pertinent records for verification of the study data. Investigators and staff will allow study monitors to inspect study facilities and documentation, and to observe the performance of study procedures. All authorized DSMB members, Health Regulatory Agencies, and other authorized personnel may inspect research records.

Site-PI Medina-Marino and other Senior Research Team members will accompany the field teams during the pretest and data collection start-up to provide immediate on-site support as needed. The teams will hold debrief sessions at the end of each field day to review progress with participant recruitment and to verify that staff have mastered use of the electronic data collection devices and data transfer.

During the course of the study, co-PIs Klausner ad Medina-Marino will maintain regular contact with field supervisors and regularly review data received. Monitoring will be done to be sure the approved protocol is being followed and to reduce the risk of a protocol violation or non-compliance. Confirmation that the study activities, study documents and the consent/assent process is being carried out as approved by the IRBs will be verified with the field supervisors. Any violations of the protocol will be immediately reported. Protocol violations will be reported in writing to all ethics committees that reviewed and approved the study in accordance with the individual committee's policy.

OVERALL STRUCTURE OF THE STUDY TEAM

This project has two PIs, who will work across all Aims.

Andrew Medina-Marino, PhD (FPD PI): is Head of FPD's Research Unit. For this project he will provide direct oversight for the South African-based study team, and will oversee and ensure quality of all in-country study implementation efforts. He has worked extensively with the Tshwane District Health Department to strengthen the clinic-lab interface, and is currently conducting an R21 study to determine the acceptability and feasibility of integrating point-of-care STI screening in ANC clinics. Dr. Medina-Marino is also the PI on a recently funded R01 grant to leverage community-based platforms to improve access and adherence to PrEP. Prior to FPD, Dr. Medina-Marino was Laboratory Branch Chief for CDC-South Africa. In this capacity, he supported and advised the South African National Health Laboratory Service (NHLS) and the National Department of Health on national point-of-care policy and guidelines.

Jeffrey Klausner, MD, MPH (UCLA PI): As the STI clinical expert on this project, he will co-lead with Dr. Medina-Marino the oversight, design, implementation, and analysis of this study. Dr. Klausner is a highly established clinical and epidemiologic researcher in STIs and HIV, and Professor of Medicine and Public Health in the UCLA Division of Infectious Diseases, School of Medicine and the Department of Epidemiology, School of Public Health. From 2009-2011 Dr. Klausner was Branch Chief for HIV and TB at the US Centers for Disease Control and Prevention in Pretoria, South Africa, helping lead the South African PEPFAR program for PMTCT, HIV care and treatment. In that role Dr. Klausner worked directly with national, provincial and district health authorities and local South African non-governmental organizations including FPD to support the scale-up of PMTCT services nationally. Dr Klausner has over 425 peer-reviewed publications, more than 20 years of NIH and CDC funded research, has been a member of the WHO STI Guidelines Committee since 2010.

There are six Co-Investigators, with the following key roles:

Susan Cleary, PhD (UCT; Co-I): For this study Dr. Cleary will oversee all cost/cost-effectiveness related activities (Aim 2). Dr. Cleary is an Associate Professor in Health Economics in the School of Public Health and Family Medicine, University of Cape Town. She has more than 15 years' experience in cost-effectiveness analysis (CEA) and decision analytic modeling. She (co)authored the first CEAs of HIV-treatment in South Africa from clinical trials, routine public primary health care settings and private practice. She also has considerable experience in studies assessing the affordability and accessibility of interventions from the patient perspective. Current projects include the cost-effectiveness of GeneXpert for TB diagnosis and behavioral interventions for mental illness in patients with HIV or diabetes.

Christina Muzny, MD, MSPH (UAB; Co-I): is an infectious diseases physician at the University of Alabama, Birmingham with expertise in translational research related to the vaginal microbiome and the pathogenesis of BV. For this project, Dr. Muzny will provide vaginal microbiome expertise, as well as guidance and support for the microbiome-related activities conducted in other laboratories. She is currently funded by a K award to perform a longitudinal vaginal microbiome study with daily vaginal specimen collection to investigate the pathogenesis of incident BV. Dr. Muzny is also working on a CCTS-funded grant to study the hypothesis that BV is an STI by comparing the genital microbiota of women with recurrent BV and their regular male sexual partner. Dr. Muzny works with a multi-disciplinary team of investigators on her vaginal microbiome studies (including Drs. Taylor and Redden) and has multiple publications in this area.

Christopher Taylor, PhD (LSU; Co-I): is an expert in the analysis and visualization of microbial communities assayed by 16S rRNA sequencing, with over 15 peer-reviewed manuscripts on this topic. During years 4 and 5, Dr. Taylor will utilize his computational resources, open source microbiome analysis software, and custom scripts and software developed in the Taylor lab for processing and analysis of the vaginal microbiome data. During years 1-3, he will provide consultation on data collection and processing for the vaginal microbiome aim. He is co-PI on a current R01 studying the relationship of the vaginal microbiota to the clearance of chlamydia, and a UH2 studying the gut microbiota in HIV-positive patients. Dr. Taylor's lab is pioneering the development of non-OTU based approaches to studying microbial communities of 16S sequencing data, and have developed the method of oligotyping for investigating potential sexual

transmission of BV-associated bacteria in monogamous couples by looking at subtle nucleotide variation. Dr. Taylor's lab has also developed software systems for analysis of high throughput sequencing data including RNA CoMPASS, PARSES, and Viamics.

David Redden, PhD (UAB; co-I): is a Professor and Vice-Chair of the Department of Biostatistics at the School of Public Health at the University of Alabama at Birmingham. He regularly collaborates with Co-Investigators Muzny and Taylor on vaginal microbiome research. For this project he will serve senior biostatistician and will be responsible for overseeing all statistical analysis for the project, including assisting with designing the permuted block randomization stratified by clinic, overseeing data management and quality control, and building the statistical models testing the association between chlamydia treatment failure in pregnant women and bacterial vaginosis (BV) associated community state types.

Robert Pattinson, MD (SA-MRC; co-I): is the director of the South African Medical Research Council's Infant Health Care Strategies Research Unit, Head of the Department of Obstetrics and Gynaecology at University of Pretoria, and internationally-recognized expert in perinatology. He is responsible for South Africa's national perinatal care and child health care surveys. For this study he will oversee the collection of specimens from mother-infant pairs admitted to hospital during and after delivery, the abstraction of medical records and discharge summaries for birth and pregnancy outcomes, and support data analysis and manuscript development relating to adverse pregnancy and birth outcomes.

Koleka Mlisana, MBChB, MMedPath (NHLS/UKZN; co-I): With over 20 years' experience as a clinical laboratory scientist and public health researcher, Dr. Mlisana will provide expert support for the implementation and operations of the GeneXpert diagnostic platform in all study clinics, ensure access to and abstraction of additional ANC and HIV-related laboratory test results from NHLS's laboratory information system, and facilitate data collection. She is Head of the Department of Medical Microbiology at NHLS, and leads NHLS's GeneXpert Working Committee.

There are also 4 consultants, each playing a specific, critical role in study implementation or analysis:

Ute Feucht, MBChB, PhD (Tshwane District DoH; Consultant): is the Tshwane District Department of Health (TDDH) Clinical Specialist Team Paediatrician, and an expert in neonatal and infant health. For this study she will facilitate and ensure access to Tshwane District ANC clinics and maternal obstetric units at local hospitals. She will also support data analysis and interpretation related to birth and neonate outcomes, and ensure ongoing support and dissemination of study findings within the leadership of TDDH.

James McIntyre, MBChB (Anova; Consultant): is an OB/GYN physician-scientist and internationally-recognized expert on HIV MTCT. He will provide consultation related to process evaluations and costing data from key stakeholders within NHLS and the National Department of Health. He will also provide support and advice as an OB-GYN and an expert in STIs, HIV, and PMTCT. He regularly serves as a consultant on these issues to the WHO, UNAIDS, and UNICEF.

Remco Peters, MD, MPH (Anova/UP; Consultant): is a clinician, epidemiologist and researcher with significant expertise in STIs and HIV clinical care and public health in resource-constrained settings. For this study, he will oversee the implementation of all microbiology and molecular epidemiology-related lab activities, provide expertise and oversight for analyzing data associated with microbiological factors and treatment outcomes, and contribute to all data analysis and dissemination activities.

Tracy Meiring, PhD (UCT; Consultant): is an Early Research Career Fellow in the Division of Medical Virology at University of Cape Town, and a geneticist with expertise in the vaginal microbiome and virome. For this project, she will provide expert scientific support and input with Drs. Muzny and Taylor in the analysis and interpretation of the microbiome data. She will also provide in country support for technical issues around microbiome specimen collection, handling and shipping.

STATISTICAL DESIGN AND POWER

Data Analysis for Aim 1: We will analyze data using R [R Foundation for Statistical Computing, Vienna, Austria] and SAS 9.4 [Cary, North Carolina]. Outcome difference among treatment arms will be assessed for statistical significance using Chi-square tests and logistic regression models for categorical/binary outcomes. Analysis of Variance (ANOVA) and multiple linear regression models will be used for continuous outcomes. Normal probability plots will be used to access the normality assumption for ANOVA and multiple linear regression models. If the normality assumption appears violated, non-parametric procedures will be utilized. All analyses will be conducted using intent-to-treat principles. Overall Type I error rate will be set at 0.05; for multiple comparisons among study arms Type I error will be set to a Bonferroni corrected Type I error of 0.01667. We will use multiple imputation of missing data when missing values exceed 10%.

Primary Outcomes to be compared among study arms, adjusted/controlling for HIV status include: 1) frequency of adverse birth outcomes (sub-Aim 1a) and 2) change in STI prevalence between baseline (1st ANC) and birth outcome (1st postnatal clinic visit, sub-Aim 1b). Secondary Outcomes: 1) prevalence and risk factors of CT, NG, and TV colonization in neonates controlling for HIV status; 2) proportion of mothers and children with STI infection at birth and risk factors for STI infection at birth, 4) factors associated with STIs at first ANC; and 5) process evaluation measures. Analytic approaches for exploratory outcomes are described within the Research Design section of the grant.

Data Analysis for Aim 3: We will analyze associations between Nugent scores, vaginal community state types (CSTs), CT treatment outcomes, vaginal pH and other clinical data. We intend to compare the relative abundance of microorganisms between cases and controls to determine which organisms are associated with persistent CT infection in pregnant women. Several statistical methods have been proposed to evaluate differential abundance in microbiome data (DESeq, DESeq2, and Voom).[144–146] Data will be analyzed at 4 time points, correlating to specimen collection. We will perform preliminary analysis at each time point to account for individual effects of different microbiota at different study stages, and to understand any time/environmental-specific differences in microbiome composition over time. CSTs will be constructed using linkage clustering of microbiome species data. Given the repeated measurements for each participant and the longitudinal nature of this aim, the primary analytic method for continuous outcome measures will be linear mixed models. For binary outcomes (infection yes/no), generalized estimating equations will be employed. Covariates for all models will be HIV status, presence/absence of specific community states, vaginal PH, and demographic variables. Other covariates affecting the microbiome (e.g. HIV status, CD4 count, ART exposure) will be included in the models to assess the effect of these factors on the treatment success rate. We will also use linear mixed models and generalized linear mixed model framework to detail the effects of individual microorganisms on CT treatment. Analytic approaches for exploratory outcomes are described within the Research Design section of the grant.

Power Calculations: Aim 1 analyses will explore intervention effects on reducing probabilities for two primary outcomes: adverse birth outcome events and change in STI prevalence at time of delivery. Based on a total sample size of approximately 2500 participants (834 participants in each study arm), calculations show that we will have at least 80% power to detect study arm absolute differences of approximately 10% or larger in the frequency of adverse birth outcomes. We conducted two sets of calculations. 1) Calculations for the probability of an adverse birth event were conducted in PASS 2008 software (https://www.ncss.com/) for differences in proportions at a single time point (i.e., birth outcome event). Calculations were run for a range of base rates ranging from 30% to 50%; this is in line with base rates from preliminary data (~40%). 2) We calculated changes in STI prevalence based on two time points (i.e., first ANC visit and birth outcome) and conducted simulation studies in two steps. Simulations used a range of pregnancy STI rates from 30% to 50%. Based on preliminary data, we anticipate that the intervention will reduce STI rates by 20% (absolute). We assumed an attrition rate of 15%.

For Aim 3, we assume 65 cases and 130 controls will provide four vaginal swabs allowing us to study the longitudinal association of vaginal microbiome characteristics and changes with persistent CT infection. Given the repeated observations within an individual, the non-independence of observations within a subject must be taken into account. Assuming an intra-class correlation coefficient of 0.20, 200 women with 4 repeated observations provide 85% power to community state prevalence of 33% among non-responses as compared to 20% among responders using a two-tailed Type I error rate of 0.05. This effect size equates to a risk ratio of 1.65, an odds ratio of 1.97.

Decision Analytic Modelling for Aim 2: Box 1 summarizes formulae for calculating costs and DALYs for the provider perspective (arguably the more complex calculation). For DALY calculations, years of life lost are the difference between age at death and average South African life-expectancy for that age; years of life with disability and disability weights will be estimated from the Global Burden of Disease studies. Deterministic sensitivity analyses will assess the impact of key parameter uncertainty (e.g. the cost of GeneXpert machines within a scale-up scenario). Probabilistic sensitivity analysis will assess uncertainty around each utilization estimate from the trial.[127] If Arm 3 costs (hypothesized to include higher costs for adverse pregnancy and birth outcomes) are greater than Arm 1 or Arm 2 costs, the intervention(s) are cost-saving and no further analysis would be required. However, if we find that the costs of Arms 1 and/or 2 exceed the costs of Arm 3, we will compute incremental costs per STI and Disability-Adjusted Life Year (DALY) averted. For the patient perspective, catastrophic expenditure will be computed by comparing patient costs to household expenditure using 10% and 20% thresholds per other South African and low and middle-income country studies.[122]

Box 1: Formulae for calculating provider costs and DALY outcomes within each study arm

Arm 1 costs = $ANCCost1 + ANCPositive_{1\text{-}n} \times (TreatCost_{1\text{-}n} + ToCCost_{1\text{-}n}) + ToCPositive^{1}_{1\text{-}n} \times (TreatCost_{1\text{-}n} + ToCCost_{1\text{-}n}) \ldots + ToCPositive^{n}_{1\text{-}n} \times (TreatCost_{1\text{-}n} + ToCCost_{1\text{-}n}) + BirthCost_{1\text{-}n} + Adversebirth_{1\text{-}n} \times AdversebirthCost_{1\text{-}n} + Adversebirthmom_{1\text{-}n} \times AdversebirthCostmom_{1\text{-}n}$

Arm 2 costs = $ANCCost1 + ANCPositive_{1\text{-}n} \times (TreatCost_{1\text{-}n}) + ANCCost2 + ANCPositive2_{1\text{-}n} \times (TreatCost_{1\text{-}n}) + BirthCost_{1\text{-}n} + Adversebirth_{1\text{-}n} \times AdversebirthCost_{1\text{-}n} + Adversebirthmom_{1\text{-}n} \times AdversebirthCostmom_{1\text{-}n}$

Arm 3 costs = $ANCCost3 + ANCPositive_{1\text{-}n} \times (TreatCost_{1\text{-}n}) + BirthCost_{1\text{-}n} + Adversebirth_{1\text{-}n} \times AdversebirthCost_{1\text{-}n} + Adversebirthmom_{1\text{-}n} \times AdversebirthCostmom_{1\text{-}n}$

Arm 1-3 DALYs* = $Adversebirth_{1\text{-}n} \times (YLLAdversebirth_{1\text{-}n} + YLDAdversebirth_{1\text{-}n} \times DWAdversebirth_{1\text{-}n}) + Adversebirthmom_{1\text{-}n} \times (YLLAdversebirthmom_{1\text{-}n} + YLDAdversebirthmom_{1\text{-}n} \times DWAdversebirthmom_{1\text{-}n})$

Key:

Full economic unit costs:

ANCCost1 = unit cost for STI testing at first ANC visit within Arm 1 and Arm 2 (point of care testing)
ANCCost2 = unit cost for STI testing at 30-34 weeks' gestation ANC visit (point of care testing)
ANCCost3 = unit cost for STI testing at first ANC visit within Arm 3 (routine laboratory testing)
$TreatCost_{1\text{-}n}$ = unit cost for STI treatment for mother and partner(s) (categorized by type of STI $_{1\text{-}n}$)
$ToCCost_{1\text{-}n}$ = unit cost for targeted ToC (categorized by type of STI $_{1\text{-}n}$)
$BirthCost_{1\text{-}n}$ = unit cost per delivery (categorized by type of delivery $_{1\text{-}n}$)
$AdversebirthCost_{1\text{-}n}$ = unit cost of treating adverse birth outcomes for neonate (categorized by type of outcome $_{1\text{-}n}$)
$AdversebirthCostmom_{1\text{-}n}$ = unit cost of treating adverse birth outcomes for mother (categorized by type of outcome $_{1\text{-}n}$)

Utilization proportions:

$ANCPositive1_{1\text{-}n}$ = Proportion of mothers positive for STI at first ANC visit (categorized by type of STI $_{1\text{-}n}$)
$ANCPositive2_{1\text{-}n}$ = Proportion of mothers positive for STI at 30-34 weeks' gestation ANC visit (categorized by type of STI $_{1\text{-}n}$)
$ToCPositive^{1}_{1\text{-}n}$ = Proportion of mothers positive for STI at first ToC (categorized by type of STI $_{1\text{-}n}$)
$ToCPositive^{n}_{1\text{-}n}$ = Proportion of mothers positive for STI at n'th ToC (categorized by type of STI $_{1\text{-}n}$)
$Adversebirth_{1\text{-}n}$ = Proportion of neonates with adverse birth outcomes (categorized by type of outcome $_{1\text{-}n}$)
$Adversebirthmom_{1\text{-}n}$ = Proportion of mothers with adverse birth outcomes (categorized by type of outcome $_{1\text{-}n}$)

DALYs:

$YLLAdversebirth_{1\text{-}n}$ = Years of life lost for adverse birth outcome for neonate (categorized by type of outcome $_{1\text{-}n}$)
$YLLAdversebirthmom_{1\text{-}n}$ = Years of life lost for adverse birth outcome for mother (categorized by type of outcome $_{1\text{-}n}$)
$YLDAdversebirth_{1\text{-}n}$ = Years of life lived with disability for adverse birth outcome for neonate (categorized by type of outcome $_{1\text{-}n}$)
$YLDAdversebirthmom_{1\text{-}n}$ = Years of life lived with disability for adverse birth outcome for mother (categorized by type of outcome $_{1\text{-}n}$)
$DWAdversebirth_{1\text{-}n}$ = Disability weight for adverse birth outcome for neonate (categorized by type of outcome $_{1\text{-}n}$)
$DWAdversebirthmom_{1\text{-}n}$ = Disability weight for adverse birth outcome for mother (categorized by type of outcome $_{1\text{-}n}$)

***While the formula for calculating DALYs is generic, we expect differences in the key proportions (e.g. adverse birth outcomes) between arms**

IDE Status

The intervention arms of this study will involve specimen collection with the GeneXpert Vaginal/ Endocervical Specimen Collection kit [Cepheid, Sunnyvale, CA] and PCR testing for CT, NG and TV using the Xpert® CT/NG and Xpert® TV cartridges [Cepheid, Sunnyvale, CA].

All of these products are FDA-approved and will be used in accordance with its labeling; therefore, this study is exempt from IDE regulations.

DISSEMINATION PLAN

Drs. Medina-Marino, Klausner, and the project team are committed to the open and timely dissemination of research outcomes from this proposed project. Staffing has been determined for this project specifically to allow for timely, high-quality analysis of all data generated, resulting in widespread, accessible dissemination of results with an eye toward high-impact strategies to influence policy-makers in low and middle-income countries.

The key staff alone on this project have been authors on more than 500 peer-reviewed journal publications, collectively. All investigators are aware of the importance of presenting findings of research in local, national and international conference settings, as well as publication in reputable journals, in order to have lasting impact on the scientific community and on affecting programs and policies that will improve health outcomes. The project team is also committed to providing results to the very community from which the data were generated; special effort will be given to making small presentations in a local, town-hall style format, and inviting members of Tshwane District in South Africa to come and share their thoughts.

Examples of conferences where these results may be shared include the South African AIDS Conference; South African National HIV Think Tank meetings; International Society for STD Research (ISSTDR) and International Union Against STIs (IUSTI) meetings; the CDC STD Prevention Conference; and various WHO Working Group meetings as appropriate.

We will seek to publish in a number of peer-reviewed journals, including *Clinical Infectious Diseases, Sexually Transmitted Diseases, Public Health Reports, PLOS Medicine,* and the *South African Medical Journal.*

Proposal Summary

Proposal Number: **Proposal Status:**
Sponsor Deadline: 02/05/2019 **Submission Method:**
Submission Type: Application

INVESTIGATOR DATA

PROJECT DIRECTOR / PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Dr.	Jeffrey		Klausner	MD

Position/Title:	Professor	**Organization:**	UCLA David Geffen School of Medicine
Department:	Medicine	**Division:**	Infectious Diseases
Street1:	9911 West Pico Blvd	**Street2:**	Suite 955
City:	Los Angeles	**County:**	Los Angeles County
State:	CA	**Zip Code:**	90035-2738
Country:	USA	**Employee ID:**	
Phone:	310-557-3044	**Fax:**	310-557-3679
Email:	JDKlausner@mednet.ucla.edu		

First Budget Period Effort: **Calendar:** 1.80 **Academic:** **Summer:**

Status of PI:
Status Waiver Required?
Signed Intellectual Property Waiver Attached?
Signed Conflict of Interest Disclosure Attached?
Agency Certification Documentation Attached?
Cost Sharing Authorization Form Attached?

SPONSOR DATA

Agency: National Institutes of Health
Proposal Type
Sponsor Mechanism: Research Project Grant (Parent R01 Clinical Trial Required)
Sponsor Type:
Sponsor Code:
Sponsor Name:
SubDivision 1:
SubDivision 2:

PROJECT DATA

Title of Project: Clinical study of STI screening to prevent adverse birth and newborn outcomes
Is This a Subcontract? No
If Yes, who is prime?
Type of Proposal:
Type of Agency: Federal
Kind of Application: New
Previous Grant # or Federal Identifier:
Change in grantee institution?
Type of Project:

PROJECT ADMINISTRATION

Who is responsible for this research?

Departmental Identification Number:	**Primary:**	**Secondary:**
Departmental Name:	**Primary:**	**Secondary:**
Primary Dept. Contact Info:		
Account Classification:	**Primary:**	**Secondary:**

Other Institutional Code:
NAICS Code:

COMPLIANCE DATA

Proposal Summary (cont'd)

Are animal subjects used? No
Is IACUC review pending?
IACUC Protocol #
IACUC Approval Date:
Are human subjects used? Yes
Is IRB review pending? Yes
IRB Protocol #
IRB Approval Date:
Does this project involve use of any of the following? Radioactive Material(s), Radiation Producing Devices(s), Recombinant DNA, Biohazardous Chemical(s), Class IIIb or IV Lasers, Other certifications of health, safety and/or environmental compliance.

BUDGET DATA

Performance Dates	Begin Date	End Date
First Budget Period:	09/01/2019	08/31/2020
Cumulative Budget Period:	09/01/2019	08/31/2024

Cost Sharing Information	Mandatory	Voluntary
Committed:		
Amount:		
Source:		

Budget Period	Direct Cost	Indirect Cost	Total Cost
Period 1:	750,375	61,589	811,964
Period 2:	914,074	24,725	938,799
Period 3:	920,958	18,892	939,850
Period 4:	924,981	37,700	962,681
Period 5:	617,838	45,324	663,162
Total:	4,128,226	188,230	4,316,456

AWARD DATA

Award #: **Contract #:** **Date:**

Budget Period	Direct Cost	Indirect Cost	Total Cost
Period 1:			
Period 2:			
Period 3:			
Period 4:			
Period 5:			
Total:			

EXPORT CONTROL

1. Will the project involve participation, collaboration or access to information by foreign nationals, defined as: individuals with foreign citizenship, foreign governments, foreign associations and corporations, or foreign political parties? Note: Foreign nationals granted US citizenship, or permanent residence "green card" or granted status as a "protected individual", e.g., political refugees and political asylum holders are "EXEMPT" from deemed export rule.
2. Will the project involve the shipment of equipment, technology, software, materials data or other information?
3. Will the project involve a foreign subcontract or other foreign contractual agreement?

COMMENTS AND EXPLANATIONS

PLEASE INDICATE ANY SPECIAL INSTRUCTIONS BELOW:

UCLA

UCLA RESEARCH
EXTRAMURAL PROPOSAL APPROVAL AND SUBMISSION SUMMARY
"EPASS"

1. Principal Investigator(s)/Co-PIs (Not Co-Investigators)

	First Name	M.I.	Last Name	Employee ID	Email Address	Extension
PI:	JEFFREY	David	KLAUSNER	604207032	jdklausner@mednet.ucla.edu	3108257225
Other PI/Co-PI:						
Other PI/Co-PI:						
Fellow *(if Individual Fellowship)*:						

Named individuals must sign certification below. Attach additional pages if needed.

2. Department or Organized Research Unit (ORU)

Administering Department Name: MEDICINE-INFECTIOUS DISEASE FS Code (Dept. Code): 1560
Account #: 441344 Cost Center: JK Recharge ID: MZ77
Dept. Contact Name: WEINBERG, MICHAEL LEE Extension: 3107943900 Email Address: mweinberg@mednet.ucla.edu
If your department/unit has a single e-mail address for all proposal/award related correspondence, enter it here:
Have the services of any campus Center or ORU been used in the development of this proposal?
If yes, select: Not Applicable
If "Other Center/Institute" is selected above, please specify name, or if multiple Center(s)/Institute(s) please add additional selection(s) here:

3. Proposal Identification

Proposal Title: Clinical study of STI screening to prevent adverse birth and newborn outcomes
Project Begin Date: 9/1/2019 Project End Date: 8/31/2024

4. Award/Proposal/Program Type

Award Type: Grant Proposal Type: New
Program Type: Applied Org Research Special Program Type: Not Applicable
If this EPASS relates to an existing Award or Master Agreement, select an Action Type:
Current Sponsor Award/ ID#:

5. Sponsor Information (Entity which will provide funding directly to UCLA)

Sponsor Name: NIH - National Institutes of Health
Sponsor Due Date: 2/5/2019 Time (Pacific):
Deadline Type:
Sponsor Guidelines and/or FOA/RFA/RFP:
☑ Yes ☐ No
Attached: ☐ URL (Section 9) ☐ Name/No. # PA-19-055
Contact (*if known*):
Email Address:
Phone #: (301) 435-1115

Prime Sponsor Information (Complete this section when UCLA is a subrecipient)

Prime Sponsor Name:
Prime Sponsor Due Date: Time (Pacific):
Prime Sponsor Guidelines and/or FOA/RFA/RFP:
☑ Yes ☐ No
Attached: ☐ URL (Section 9) ☐ Name/No. #
Contact (*if known*):
Email Address:
Phone #:

6. Proposal Checklist - *Carefully Review and Answer All Questions*

Yes	No	
☐	☑	PI Exception Required? (Check Requirements and Look up Eligibility). If yes, attach approval form (Sample Approval Form)
☑	☐	On Campus Space? Indicate location: Building: Center for Health Science Room: 52-256
☐	☑	Off Campus Space? Indicate location:
☑	☐	Outgoing Agreements? If yes, provide entity names in Section 9, Remarks, and attach Sub-recipient Commitment Form(s) or FDP Expanded Clearinghouse Subrecipient Letters(s) of Intent for each entity. PI signature below indicates review and approval of cost reasonableness. (See Outgoing Subawards Overview)
☑	☐	Does this project involve activities outside the U.S. or partnership with International Collaborators?
☐	☑	**Is any Cost Sharing/Matching proposed in this application? (Cash, unfunded effort, or in-kind contributions - do not include salary cap differential.) If Yes, required by sponsor?** ☐ Yes (mandatory committed) ☐ No (voluntary committed) Cost Share Amount: Source/FAU#:
☐	☑	**Is any unfunded effort proposed in this application? In accordance with UC Policy**, "unfunded effort", must be reported in ERS.(**Do not include salary cap differential here)** Source/FAU#:
☐	☑	Do you anticipate program income? If yes, specify:

☐	☑	**Does this proposal involve the use of significant IT resources (beyond basic academic infrastructure); the generation of datasets or digital assets; or a budget with over $10,000 in IT-related hardware, software, or staff expenditures?** (Check additional requirements)
☑	☐	**Human Subjects?** If yes, indicate "Pending", IRB # or Exemption #: Pending Delayed Onset ☐
☐	☑	**NIH-funded Clinical Trial?** If yes, investigators and staff involved in the conduct, oversight, or management of clinical trials should be trained in Good Clinical Practice. Training is available through CITI Program. Provide names on the next page.
☐	☑	**Will the clinical research study utilize UCLA Health System resources, including but not limited to, any patient care costs? If yes, then a Policy 915 Coverage Analysis is required (contact coverageanalysis@mednet.ucla.edu).**
☐	☑	**Animal Subjects?** If yes, indicate "Pending" or ARC#: Delayed Onset ☐
☐	☑	**Human Embryonic Stem Cell Research?** If yes, refer to the Stem Cell Policy and Procedures.
☐	☑	**Non-UCLA materials/equipment to be used?** If yes, indicate type: Source:
☐	☑	**Human or primate cells, tissue, or fluids; recombinant or synthetic nucleic acids; potentially infectious materials; exotic plants or plant pathogens; select agents or toxins?** For more information, see IBC website.
☐	☑	**Use of UC IP?** If yes, specify case number:

Yes	No	**Export Control (see RPC Website) – Does the project involve the following:**
☐	☑	**Shipping or carrying any tangible object or item to a foreign country?** If yes, specify:
☑	☐	**Conducting research or other activities in, taking money to or planning to have money transferred to a foreign country?** If yes, specify: Subaward to South Africa
☐	☑	**Training foreign persons in using equipment, technology, or technical data?** If yes, specify:
☐	☑	**Traveling to or doing research in a country currently under a US Trade or Economic Embargo (See OFAC Website)?** If yes, specify:

7. Additional Forms Required

Yes	No	**COI (Disclosure Requirements)**
☑	☐	**Sponsor/Prime Sponsor is Federal Public Health Service (PHS) or agency that has adopted the PHS regulations? If yes, provide names of other investigators on page 3 (See UCLA Policy 926).**
☐	☑	**Sponsor/Prime Sponsor is Federal (other than PHS), CIRM or special research programs managed by the UC Research Grants Program Office (RGPO)?** If yes, attach COI Form 740 & Supplement to Form 740 (if applicable). **See** UCLA Procedure 925.3.
☐	☑	**Non-Government Sponsor/Prime Sponsor?** If yes and project is ***Research***, attach Form 700-U, 700-U Addendum and 700-U Supplement, as applicable, unless sponsor is exempt. **See** UCLA Procedure 925.2

Yes	No	**Industry Sponsored Research**
☐	☑	**Industry Sponsored Non-Clinical Proposal?** If yes, attach Industry Sponsored Research Checklist.
☐	☑	**Industry Sponsored Clinical Trial?** If yes, view the Clinical Trials Contracts & Strategic Relations Checklist to determine additional required attachments.

8. Funds Requested

1st Budget Period

Direct Costs ($): 710,955 Excluded Direct Costs ($): 590,255 F&A Costs ($): 67,592 Total Costs ($): 778,547

All Project Periods (*complete only when multiple budget periods are involved*)

Direct Costs ($): 4,152,453 Excluded Direct Costs ($): 3,816,405 F&A Costs ($): 188,187 Total Costs ($): 4,340,640

F&A: F&A Rate (%): 56 F&A Base Type: MTDC If Other, specify:

9. Remarks

Subawards to UAB, LSU, and FPD

10. Accepts Responsibility

The Investigator(s) certifies to the following: (1) that the information submitted within this application is true, complete and accurate to the best of their knowledge; (2) that any false, fictitious, or fraudulent statements or claims may subject the Investigator(s) to criminal, civil or administrative penalties; (3) agrees to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of the application; and (4) that you are not currently debarred, suspended or ineligible to receive federal or non-federal funds; (5) all Clinical Trials based upon FDAAA 801, will be registered in ClinicalTrials.gov. When multiple Investigators are proposed in an application this assurance must be obtained by all named Investigators.

Approved Electronically by JEFFREY David KLAUSNER 1/24/2019
Principal Investigator (Required) Date

Approved Electronically by RAELLEN GARIFE MAN 1/29/2019
DRA Date

Date

Approvals: Includes Certifications

Approved Electronically by JUDITH Silverstein CURRIER 1/28/2019
Chair/ORU Director/Dean/Medical Center Director (Required) Date

Date

Date

For proposal submissions funded by Federal Public Health Service (PHS) or an agency that has adopted the PHS regulations, provide, below, the name and email address for all project personnel responsible for the design, conduct, or reporting of research. All named individuals must have a current disclosure in eDGE, which is accessed at coi.research.ucla.edu.

☐ **No other project personnel responsible for the design, conduct, or reporting of research.**

First Name	M.I.	Last Name	Email Address	eDGE Disclosure Date
Jeffrey	D	Klausner	jdklausner@mednet.ucla.edu	9/24/18

For NIH-funded clinical trials, provide names of all investigators and staff involved in the conduct, oversight, or management of the project. Recipients of GCP training are expected to retain documentation of their training.

First Name	M.I.	Last Name	Email Address	GCP Training Completion Date

University of California, Los Angeles | Office of Contract and Grant Administration

Subrecipient vs. Contractor Determination Checklist

The following checklist must be analyzed and filled out per OCGA process and the Uniform Guidance 200.330 in order to determine whether the agreement between UCLA and the third party receiving funds constitutes a Subrecipient or a Contractor (Vendor). Submit completed form to the UCLA Office of Contract and Grant Administration (OCGA/Department Research Administrator (DRA) at the proposal stage (before submission of proposal). NOTE: This form is not required for Multi-Campus Awards

UCLA PI: Jeffrey Klausner PATS Number (if available): _____

Third Party Name: Foundation for Professional Development

Third Party PI: Andrew Medina-Marino

Project Title: Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes

Prime Sponsored by (e.g. federal agency, non-profit organizations etc.): NIH

SUBRECIPIENT: A subaward is for the purpose of a third party to carry out a portion of an award and creates an assistance relationship between UCLA and the third party. Characteristics which support the classification of the third party entity as a subrecipient include when the third party (check all that apply):

- ☒ Performance represents an intellectually significant portion of the overall programmatic effort and is measured against the objectives of the program;
- ☒ There is an identified principal investigator for the subrecipient who has responsibility for making programmatic decisions;
- ☐ Work could result in the development of intellectual property;
- ☒ Is expected to author or co-author publications on the results of program/project work;
- ☒ Will need animal and/or human subject approval for its work;
- ☐ Provides cost sharing or matching funds;
- ☒ Will use the funds to carry out a program for a public purpose, as opposed providing goods or services for the benefit of the pass-through entity (i.e. UCLA).

Entities that include these characteristics are responsible for adherence to applicable program requirements specified in the Award

CONTRACTOR (VENDOR): A contract is for the purpose of obtaining goods and services for UCLA's own use and creates a procurement relationship between UCLA and the third party contractor. Characteristics indicative of a procurement relationship between UCLA and a contractor are when the third party receiving the funds (check all that apply):

- ☐ Provides the goods and services within normal business operations;
- ☐ Provides similar goods or services to many different purchasers;
- ☐ Performs a series of repetitive tests or activities requiring little or no discretionary judgment;
- ☐ Normally operates in a competitive environment;
- ☐ Provides goods or services that are ancillary to the operation of the program; and

Entities that include these characteristics are NOT subject to compliance requirements of the program as a result of the agreement, though similar requirements may apply for other reasons.

Description: *All of the characteristics listed above may not be present in all cases. Therefore, judgment must be used in classifying the agreement as either a subaward or a procurement contract. In determining whether an agreement constitutes a subaward or a procurement contract, the substance of the relationship is more important than the form of the agreement.*

Based on your analysis of the above checklist results, the organization is determined to be a

☒ **SUBRECIPIENT *** ☐ **CONTRACTOR (VENDOR)**

Digitally signed by Jeffrey D. Klausner
DN: cn=Jeffrey D. Klausner, o=UCLA, ou=UCLA David Geffen School of Medicine and Fielding School of Public Health, email=JDKlausner@mednet.ucla.edu, c=US

1/14/19

UCLA Principal Investigator Signature **Date**

***Submit this form along with Subrecipient Commitment Form as part of the proposal package for the minimum requirements**

ORA/DRA REVIEW:

☐ AGREE ☐ DISAGREE, RETURN TO DEPT COMMENTS _____

Name of Authorized Institution Official (e.g. DRA, OCGA) _____

Signature of Above Authorized Institution Official _____ Date _____

Attachment B

University of California, Los Angeles — Office of Contract and Grant Administration

SUBRECIPIENT COMMITMENT FORM

All Subrecipients must complete this form when submitting a proposal to UCLA. It provides a checklist of documents and certifications required by sponsors and it must be endorsed by the authorized institutional representative prior to proposal submission.

Subrecipient's Legal Name: Foundation for Professional Developmennt

Subrecipient's Principal Investigator: Dr Andrew Medina-Marino

UCLA's Principal Investigator: Jeffrey D. Klausner Prime Sponsor: National Institutes of Health

UCLA's Proposal Title: Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes

Subrecipient Total Funds Requested: $3,403,260 Performance Period Begin Date: Sept 1, 2019 End Date: Aug 31, 2024

Section A: Proposal Documents – ALSO SEE SECTION E (pg.5); Answer the questions and if categorized as a Subrecipient continue to fill out the rest of the form.

The following documents are included in our subaward proposal submission and covered by the certifications below:

- ☒ STATEMENT OF WORK (Required)
- ☒ BUDGET AND BUDGET JUSTIFICATION (Required)
- ☒ SUBRECIPIENT COMMITMENT FORM (This form)

Section B: Certifications

1. **Facilities & Administrative Rates** included in this proposal have been calculated based on the following:
   - ☐ Our federally recognized negotiated F&A rates for this type of work. If this box is checked, a copy of your F&A rate agreement *must* be furnished to UCLA Office of Contract & Grant Administration (OCGA).
   - ☒ A reduced F&A rate dictated by the prime sponsor that we hereby agree to accept. Rate: 8% Base Type: Foreign entity
   - ☐ Not applicable (No indirect costs are requested by Subrecipient).

2. **Fringe Benefit Rates** included in this proposal have been calculated based on the following:
   - ☐ Rates are consistent with our Federally negotiated rates. If this box is checked, a copy of your Federal fringe benefit rate agreement *must* be furnished to UCLA OCGA.
   - ☒ Other rates as specified in Section F: Comments (please specify the basis on which the rate has been calculated)

3. **Human Subjects** YES ☒ NO ☐
   If **YES** copies of the following documentation must be provided before any subaward can be issued:
   1) IRB approval certification
   2) IRB approved project protocol
   3) Approved "Informed Consent" form
   4) Verification of IRB training
   5) Verification of FWA number and Expiration date

   Please forward these documents to UCLA's Principal Investigator as soon as they become available.
   If **YES** and NIH funding is involved:
   - Have all key personnel completed human subjects training at the subrecipient's institution? YES ☒ NO ☐
   - Please attach a list of key personnel who are on this project on a separate sheet.

4. **Animal Subjects** YES ☐ NO ☒
   If **YES**, a copy of the IACUC approval must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available.
   If **YES** and NIH funding is involved:
   Please provide your institution's PHS Assurance number. PHS Assurance No.: _____ Expiration Date: _____
   If you do not have one on file, you will need to apply for one and provide it to us before any subaward will be issued.

5. **Stem Cells** YES ☐ NO ☒
   If **YES**, a copy of the Stem Cell approval must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available.

6. **Dual Use Research of Concern (DURC)** (Applicable to projects funded by PHS/NIH)

☒ Not applicable.

Will this project use one or more of the following agents or toxins (Check all that apply)?

☐ Marburg virus	☐ Reconstructed 1918 Influenza virus	☐ Avian influenza virus (highly pathogenic)
☐ Variola minor virus	☐ Variola major virus	☐ Toxin-producing strains of Clostridium botulinum
☐ Rinderpest virus	☐ Yersinia pestis	☐ Bacillus anthracis
☐ Botulinum neurotoxin	☐ Francisella tularensis	☐ Foot-and-mouth disease virus
☐ Burkholderia mallei	☐ Burkholderia pseudomallei	☐ Ebola virus

If at least one box is checked, a copy of your Institution's Review Entity determination as to whether the research qualifies as DURC must be provided. Once we receive it, and it is determined by PHS/NIH that the research is in fact DURC; a copy of the mitigation plan must be provided to UCLA before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available. For more information, please see NIH Guide notice NOT-OD-15-017.

7. **Genomic Data Sharing Policy** (Applicable to projects funded by PHS/NIH, see announcement NOT-OD-14-124) **YES** ☐ **NO** ☒

If **YES**, a copy of the Institutional Certification for large-scale human genomic data must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available. Additionally, investigators are expected to make all large scale data (human and non-human) publicly available through a data repository (e.g. dbGaP, GEO, SRA).

8. **Cost Sharing** **YES** ☐ if **YES**, $_____ **NO** ☒

If **YES**, explanation of Cost Sharing sources *must* be included in the subrecipient's budget. Please note that an annual verification of cost share commitment will be required.

9. **National Science Foundation (NSF) Conflict of Interest**

Applicable to NSF, including NSF flow-through or any other program *except PHS/NIH* requiring Federal Financial disclosure.

☒ Not applicable because this project is not being funded by NSF or any other program requiring Federal Financial disclosure.

☐ Subrecipient organization/institution hereby certifies that it has an active and enforced policy on conflict of interest consistent with the provision of NSF Award & Administration Guide Chapter IV.A.

10. **Public Health Service (PHS) Financial Conflict of Interest**

Applicable to projects funded by PHS/NIH, or any other program requiring DHHS Financial Conflict of Interest (FCOI) disclosure.

☐ Not applicable because this project is not being funded by PHS/NIH or any other program requiring DHHS FCOI.

☒ Subrecipient organization/institution hereby certifies that it has an active and enforced policy on conflict of interest consistent with the provision of 42 CFR Part 50 Subpart F.

☐ My organization **DOES NOT HAVE** a PHS compliant policy in place but will have one at the time of award.
(A sample FDP FCOI policy can be found at http://sites.nationalacademies.org/PGA/fdp/PGA_061001).
List the names of individuals working on this project that is responsible for the design, conduct, or reporting of the research.
Each individual listed MUST fill out and attach the PHS Financial Disclosure form.

11. **National Science Foundation (NSF) Ethics in Research Training**

Applicable to projects funded by NSF or any other programs requiring Ethics in Research Training.

☒ Not applicable because this project is not being funded by NSF or any other programs requiring Ethics in Research Training.

☐ Subrecipient organization/institution hereby certifies that it will ensure that all undergraduates, graduate students, and postdoctoral researchers who will be supported by this NSF proposal will be trained on the oversight in the responsible and ethical conduct of research.

12. **Public Health Service (PHS) Research Misconduct**

Applicable to projects funded by PHS/NIH

☐ Not applicable because this project is not being funded by PHS/NIH.

☒ Subrecipient organization/institution hereby certifies that it has completed and submitted the "Assurance of Compliance by Sub-Award Recipients available at: http://ori.hhs.gov/sites/default/files/PHS-6315.pdf

13. **Certification of Debarment, Suspension, Proposed Debarment**

Is the Subrecipient Entity, Subrecipient PI, or any other employee or student participating in this project, debarred, suspended or otherwise excluded from or ineligible for participation in federal assistance programs or activities? **YES** ☐ **NO** ☒

If **YES**, please explain in Section F: Comments.

Subawards to any entity or individual include in the Federal Excluded Parties are prohibited.

If **NO**, the Organization Certifies they: (answer all questions below)

☐ are ☒ are not presently debarred, suspended, proposed for debarment, or declared ineligible for award of federal contracts

☐ are ☒ are not presently indicted for, or otherwise criminally or civilly charged by a government agency.

☐ have ☒ have not within three (3) years preceding this offer, been convicted of or had a civil judgment rendered against them for commission of fraud or criminal offense in connection with obtaining , attempting to obtain, or performing a public (federal, state, or local) contract or subcontract; violation of Federal or State antitrust statutes relating to the submission of offers, or commissions of contract or subcontract; violation of Federal or State antitrust statutes relating to the submission of offers, or commission of embezzlement, theft, forgery, bribery, falsification, or destruction of records, making false statements or receiving stolen property.

☐ have ☒ have not within 3 years preceding this offer, had one or more contracts terminated for default by any federal agency.

14. Subrecipient is what type of entity? Non-domestic (non-US) Entity

Is the Subrecipient a for-profit entity? **YES** ☒ **NO** ☐

If **YES**, UCLA PI should complete the Fair and Reasonable Cost Analysis and attach it to this form.

Section C: Audit Status

1. Does the subrecipient receive an annual audit in accordance with OMB Circular A-133/Uniform Guidance? **YES** ☒ **NO** ☐

If **YES**,

a) A complete copy of subrecipient's most recent audit report, or the Internet URL link to a complete copy, must be furnished to UCLA OCGA before a subaward will be issued.

b) Has the audit been completed for the most recent fiscal year? **YES** ☒ **NO** ☐

c) Were there any audit findings reported? **YES** ☐ **NO** ☒

If **YES**, UCLA requires that the entity complete the Certificate of Compliance

If **NO**, UCLA requires that the entity complete a Financial Audit Management Questionnaire and may require a limited-scope audit before a subaward can be issued.

Section D: Subrecipient Institutional Information

1. Location of Subrecipient

Address: 173 Mary Road

City, State, Zip: The Willows, Pretoria, South Africa Congressional District: N/A

Primary Place of Performance *(If primary place of performance is different than Location of Subrecipient)*

Address: _____

City, State, Zip: _____ Congressional District: _____

2. Subrecipient DUNS Number: 568904572

3. Subrecipient EIN Number: 1900217648A1

4. Subrecipient NAICS Code: 611430

5. Is Subrecipient owned or controlled by a parent entity? **YES** ☐ **NO** ☒ If **YES**, provide information for the parent entity below:

Address: _____

City, State, Zip: _____ Congressional District: _____

Parent DUNS Number: _____

Parent EIN Number: _____

6. Is subrecipient currently registered in System for Award Management (SAM)? (www.sam.gov) **YES** ☒ **NO** ☐
   If **NO**, organizations that have not registered with SAM will need to obtain a DUNS number first and then access the online registration through the SAM (System for Award Management) home page at https://www.sam.gov (U.S. organizations will also need to provide an Employer Identification Number from the Internal Revenue Service that may take an additional 2-5 weeks to become active). Completing and submitting the registration takes approximately one hour to complete and your SAM registration will take 3-5 business days to process. **Subrecipient *must have* a current SAM registration and maintain their current information in SAM prior to issuance of a Subaward.**

7. Is the Subrecipient's Principal Investigator and/or any other Investigator (key personnel) on the proposed subaward a UCLA student (undergraduate or graduate), postdoctoral scholar, or other trainee, or a faculty or staff employee? **YES** ☐ **NO** ☒
   If **YES,** please describe the relationship in Section F: Comments and notify the OCGA Subaward Team at ocgasubawards@em.ucla.edu.

8. Federal Funding and Accountability Transparency Act (FFATA)
   Provide the names and total compensation of the five (5) most highly compensated officers of the subrecipient entity if:
   a. The recipient in its preceding fiscal year received:
      i. 80 percent or more of its annual gross revenues in Federal awards; **AND**
      ii. $25,000,000 or more in annual revenues from the Federal awards; **AND**
   b. The public does NOT have access to information about the compensation of the senior executives of the entity through periodic reports filed under section 13(a) or 15(d) of the Securities and Exchange Act of 1934 (15 U.S. C. 78m(a), 78o(d) or section 6104 of the Internal Revenue Service Code of 1986 [26 USC 6104]

   If **YES** to a and b: Attach List
   If **NO** to a and/or b: Check this box ☐
   Note: "Total compensation" means the cash and noncash dollar value earned by the executive during the subrecipient's past fiscal year of the following (for more information see 17 CFR 229.402 (c)(2)).

   1) Salary and Bonus
   2) Award of stock, stock options, and stock appreciation rights. Use the dollar amount recognized for financial statement reporting purposes with respect to the fiscal year in accordance with FAS 123R
   3) Earnings for services under non-equity incentive plans. Does not include group life, health, hospitalization, or medical reimbursement plans that do not discriminate in favor of executives, and are available generally to all salaried employees.
   4) Change in pension value. This is the change in present value of defined benefit and actuarial pension plans.
   5) Above-market earning of deferred compensation which are not tax-qualified
   6) Other compensation. For Example, severance, termination payments, value of life insurance paid on behalf of the employee, perquisites or property if the values for the executive exceed $10,000

   Project Description: In compliance with FFATA reporting obligations, please provide a succinct description of the overall purpose and expected outcomes. This information will be displayed on the https://www.USAspending.gov website and will be available to the general public.

STIs are common in pregnant women but often go undiagnosed; we recently found a 41% STI prevalence amongst HIV-infected pregnant women, of which 64% of infections were asymptomatic. Recent research suggests the vaginal microbiome may play a critical role in STI acquisition, persistence and treatment outcomes. Our pilot work has shown that diagnostic testing for CT, NG, and TV in antenatal care services for HIV-infected pregnant women in South Africa is highly acceptable and feasible; however, our work has made clear that evaluating the impact and cost effectiveness of different diagnostic screening strategies that optimally decrease the burden of STIs during pregnancy and at time-of-delivery is urgently needed. Furthermore, our findings highlight that biological factors that increase the risk for STI persistence and/or treatment failures must be further investigated. In response to the need to 1) identify cost effective screening strategies that optimally decrease the burden of STIs during pregnancy, and reduce adverse pregnancy and infant outcomes, 2) elucidate the role of the vaginal microbiome in treatment outcomes, and 3) inform STI screening and treatment guidelines in other low-middle income countries, we propose a the following three Aims: Aim 1: Evaluate different diagnostic screening interventions to decrease the burden of CT/NG/TV, and reduce adverse pregnancy and birth outcomes among pregnant women. Aim 2: Evaluate the cost per pregnant women diagnostically screened, and the cost-effectiveness per STI averted at time of delivery and adverse birth outcome Aim 3: Investigate the relationship between the vaginal microbiome and STI treatment outcomes.

Section E: Subrecipient Requirements and Responsibilities

Before submitting a subaward proposal, the subrecipient must verify that it fits the characteristics of a subrecipient, rather than those of a contractor. The following chart outlines the differences. Please check all that apply.

Subrecipient	Contractor
☒ Performance represents an intellectually significant portion of the overall programmatic effort and is measured against the objectives of the Federal program	☐ Provides goods or services that are ancillary to the operation of the Federal program
☒ Will use the Federal funds to carry out a program for a public purpose, as opposed to providing goods or services for the benefit of UCLA	☐ Provides the goods or services purchased with the Federal funds within normal business operations
☒ Is responsible for adhering to applicable Federal program requirements specified in the Federal award	☐ Provides similar goods or services to many different purchasers
☒ There is an identified principal investigator for the subrecipient who has responsibility for making programmatic decisions	☐ Is not subject to the compliance requirements of the Federal program as a result of the agreement with UCLA
	☐ Normally operates in a competitive environment

☒ YES ☐ NO My organization is properly categorized as a subrecipient as described above.

If "No," please contact the UCLA PI about procuring your organization's products and services as a contractor.

Section F: Comments (please attach additional pages if necessary)

FPD's fringe benefits rates are based on internal policies, and are specified in the detailed budget.

Approved for Subrecipient

The information, certifications, and representations above have been read, signed, and made by an authorized institutional representative of the Subrecipient named herein. The appropriate programmatic and administrative personnel involved in this application are aware of agency policies in regard to subawards and are prepared to establish the necessary inter-institutional agreements consistent with those policies. Any work begun and/or expenses incurred prior to execution of a subaward agreement are at the Subrecipient's own risk.

Signature of Subrecipient's Authorized Institutional Representative	173 Mary Road, The Willows Street Address
Henk Reeder Typed Name of Subrecipient's Authorized Institutional Representative	Pretoria, Gauteng, South Africa City, State, Zip
Chief Operating Officer Title of Subrecipient's Authorized Institutional Representative	+27128169000 (Phone) +27 86 567 0253 (Fax)
January 27, 2019 Date	henkr@foundation.co.za Email Address

UCLA OCGA Office of Contract and Grant Administration

FDP EXPANDED CLEARINGHOUSE PILOT SUBRECIPIENT LETTER OF INTENT

This can ONLY be used in lieu of the UCLA OCGA Subrecipient Commitment Form by Institutions who are listed as part of the FDP Expanded Clearinghouse Pilot at: *https://fdpclearinghouse.org/organizations*

Subrecipient (Sub) Legal Name:	University of Alabama at Birmingham	Pass-Through Entity (PTE) Legal Name:	The Regents of the University of California, Los Angeles
Sub DUNS:	063690705	PTE DUNS:	092530369

Information above must match FDP Expanded Clearinghouse Pilot Entity Profile

Sub Principal Investigator:	Christina Muzny, MD, MSPH	PTE Principal Investigator:	Jeffery Klausner, MD
Sub Internal Project Identifier *(optional)*:		PTE Internal Project Identifier *(ex. PATS #)*:	

Project Title:	Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes		
Prime Awarding Agency:	NIH	Complete Project Period:	*Start:* 9/1/2019 *End:* 8/31/2024
Total Proposed Amount for Complete Project Period:	$ 315,082	Cost Sharing Amount for Complete Project Period:	$ 0

If Cost Sharing, a separate cost share budget and justification should be attached

***Project Facilities & Administrative Rates** (check one):*

☒ Federally negotiated F&A rate that matches our FDP Expanded Clearinghouse Pilot Entity Profile
☐ A reduced F&A rate dictated by the prime awarding agency. Rate:_____ Base Type:_____
☐ Not applicable (no indirect costs are requested by Sub)

Project Use Information:

Human Subjects ☐ Yes ☒ No	Animal Subjects ☐ Yes ☒ No	Stem Cells ☐ Yes ☒ No	Genomic Data Sharing ☐ Yes ☒ No

If Yes, please forward approval(s) to PTE PI as soon as available as approval(s) must be provided before any subaward can be issued

Institutional Authorized Official Information:

Sub Name/Title:	Melinda Cotten, Asst VP Sponsored Programs	PTE Name/Title:	Mary Haskins, AO/SO
Sub Phone:	205-934-5266	PTE Phone:	310-794-0622
Sub Email:	osp@uab.edu	PTE Email:	MHaskins@research.ucla.edu
Sub Email for Awards (if different from above):			

Sub *Place of Performance* the same as FDP Expanded Clearinghouse Pilot Entity Profile's: ☒ Yes ☐ No (for FFATA reporting purposes)

This proposal has been reviewed and approved by the appropriate official(s) of Subrecipient, and certified to its accuracy and completeness. The appropriate programmatic and administrative personnel of Subrecipient involved in this application are aware of the prime awarding agency's policies, agree to accept the obligation to comply with award terms, conditions and certifications, and are prepared to establish the necessary inter-institutional agreement consistent with that policy.

The following documents are attached to this Statement of Intent:

☒ Sub Statement of Work (required)
☒ Sub Budget Justification (required)
☐ Sub Detailed Line Item Budget (required)
☐ Other: _____

for 1/28/19

Signature of Subrecipient's Authorized Official — Date

Melinda Cotten, Assistant VP of Sponsored Programs

Name and Title of Authorized Official

Form **W-9**
(Rev. October 2018)
Department of the Treasury
Internal Revenue Service

Request for Taxpayer Identification Number and Certification

▶ **Go to *www.irs.gov/FormW9* for instructions and the latest information.**

Give Form to the requester. Do not send to the IRS.

Print or type. See Specific Instructions on page 3.

1 Name (as shown on your income tax return). Name is required on this line; do not leave this line blank.

University of Alabama at Birmingham

2 Business name/disregarded entity name, if different from above

3 Check appropriate box for federal tax classification of the person whose name is entered on line 1. Check only **one** of the following seven boxes.

☐ Individual/sole proprietor or single-member LLC ☐ C Corporation ☐ S Corporation ☐ Partnership ☐ Trust/estate

☐ Limited liability company. Enter the tax classification (C=C corporation, S=S corporation, P=Partnership) ▶

Note: Check the appropriate box in the line above for the tax classification of the single-member owner. Do not check LLC if the LLC is classified as a single-member LLC that is disregarded from the owner unless the owner of the LLC is another LLC that is **not** disregarded from the owner for U.S. federal tax purposes. Otherwise, a single-member LLC that is disregarded from the owner should check the appropriate box for the tax classification of its owner.

☑ Other (see instructions) ▶ State University - 501(c)(3) Nonprofit Organization

4 Exemptions (codes apply only to certain entities, not individuals; see instructions on page 3):

Exempt payee code (if any)

Exemption from FATCA reporting code (if any)

(Applies to accounts maintained outside the U.S.)

5 Address (number, street, and apt. or suite no.) See instructions.

701 20th Street South - AB 921

Requester's name and address (optional)

6 City, state, and ZIP code

Birmingham, AL 35294-0109

7 List account number(s) here (optional)

Part I Taxpayer Identification Number (TIN)

Enter your TIN in the appropriate box. The TIN provided must match the name given on line 1 to avoid backup withholding. For individuals, this is generally your social security number (SSN). However, for a resident alien, sole proprietor, or disregarded entity, see the instructions for Part I, later. For other entities, it is your employer identification number (EIN). If you do not have a number, see *How to get a TIN*, later.

Note: If the account is in more than one name, see the instructions for line 1. Also see *What Name and Number To Give the Requester* for guidelines on whose number to enter.

Social security number

			-			-				

or

Employer identification number

6	3	-	6	0	0	5	3	9	6	

Part II Certification

Under penalties of perjury, I certify that:

1. The number shown on this form is my correct taxpayer identification number (or I am waiting for a number to be issued to me); and
2. I am not subject to backup withholding because: (a) I am exempt from backup withholding, or (b) I have not been notified by the Internal Revenue Service (IRS) that I am subject to backup withholding as a result of a failure to report all interest or dividends, or (c) the IRS has notified me that I am no longer subject to backup withholding; and
3. I am a U.S. citizen or other U.S. person (defined below); and
4. The FATCA code(s) entered on this form (if any) indicating that I am exempt from FATCA reporting is correct.

Certification instructions. You must cross out item 2 above if you have been notified by the IRS that you are currently subject to backup withholding because you have failed to report all interest and dividends on your tax return. For real estate transactions, item 2 does not apply. For mortgage interest paid, acquisition or abandonment of secured property, cancellation of debt, contributions to an individual retirement arrangement (IRA), and generally, payments other than interest and dividends, you are not required to sign the certification, but you must provide your correct TIN. See the instructions for Part II, later.

Sign Here Signature of U.S. person ▶ Stephanie Mullins Date ▶

UAB Vendors:

Please note that the address above is for tax purposes only. All correspondence, including invoices and payments, should be directed to the UAB department with whom you have a business relationship and whose contact information is:

Department Name: _____

Department Contact: _____

Department Mailing Address: _____

_____

_____

COLLEGES AND UNIVERSITIES RATE AGREEMENT

EIN: 1636005396A6

ORGANIZATION:
University of Alabama at Birmingham
921 Administration Building 701 20th Street South
Birmingham, AL 35294-0109

DATE:09/13/2017

FILING REF.: The preceding agreement was dated 09/01/2016

The rates approved in this agreement are for use on grants, contracts and other agreements with the Federal Government, subject to the conditions in Section III.

SECTION I: INDIRECT COST RATES

RATE TYPES: FIXED FINAL PROV. (PROVISIONAL) PRED. (PREDETERMINED)

	EFFECTIVE PERIOD				
TYPE	FROM	TO	RATE(%)	LOCATION	APPLICABLE TO
PRED.	10/01/2015	09/30/2016	47.00	On-Campus	Organized Research
PRED.	10/01/2016	09/30/2019	48.50	On-Campus	Organized Research
PRED.	10/01/2015	09/30/2019	45.00	On-Campus	Instruction
PRED.	10/01/2015	09/30/2019	36.00	On-Campus	Other Sponsored Activities
PRED.	10/01/2016	09/30/2019	5.40	On-Campus	(1) IPA
PRED.	10/01/2015	09/30/2019	26.00	Off-Campus	All Programs
PROV.	10/01/2019	Until Amended			Use same rates and conditions as those cited for fiscal year ending September 30, 2019.

*BASE

Modified total direct costs, consisting of all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel and up to the first $25,000 of each subaward (regardless of the period of performance of the subawards under the award). Modified total direct costs shall exclude equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and fellowships, participant support costs and the portion of each subaward in excess of $25,000. Other items may only be excluded when necessary to avoid a serious inequity in the distribution of indirect costs, and with the approval of the cognizant agency for indirect costs.

SECTION I: FRINGE BENEFIT RATES**

TYPE	FROM	TO	RATE(%)	LOCATION	APPLICABLE TO
FIXED	10/1/2017	9/30/2018	30.20	University	Faculty
FIXED	10/1/2017	9/30/2018	9.80	University	Part-time, Temporary & Irregular
FIXED	10/1/2017	9/30/2018	16.10	University	Post Docs
FIXED	10/1/2017	9/30/2018	35.40	University	All Others
FIXED	10/1/2017	9/30/2018	15.40	Hospital	Part-time, Temporary & Irregular
FIXED	10/1/2017	9/30/2018	18.40	Hospital	Residents, Fellows & Post Docs
FIXED	10/1/2017	9/30/2018	34.60	Hospital	All Others
PROV.	10/1/2018	Until amended			Use same rates and conditions as those cited for fiscal year ending September 30, 2018.

** DESCRIPTION OF FRINGE BENEFITS RATE BASE:

Salaries and Wages

Part-time Temporary/Irregular are not being combined with Students. The University has elected to waive any recovery for the Students.

SECTION III: GENERAL

A. LIMITATIONS:

The rates in this Agreement are subject to any statutory or administrative limitations and apply to a given grant, contract or other agreement only to the extent that funds are available. Acceptance of the rates is subject to the following conditions: (1) Only costs incurred by the organization were included in its facilities and administrative cost pools as finally accepted: such costs are legal obligations of the organization and are allowable under the governing cost principles; (2) The same costs that have been treated as facilities and administrative costs are not claimed as direct costs; (3) Similar types of costs have been accorded consistent accounting treatment; and (4) The information provided by the organization which was used to establish the rates is not later found to be materially incomplete or inaccurate by the Federal Government. In such situations the rate(s) would be subject to renegotiation at the discretion of the Federal Government.

B. ACCOUNTING CHANGES:

This Agreement is based on the accounting system purported by the organization to be in effect during the Agreement period. Changes to the method of accounting for costs which affect the amount of reimbursement resulting from the use of this Agreement require prior approval of the authorized representative of the cognizant agency. Such changes include, but are not limited to, changes in the charging of a particular type of cost from facilities and administrative to direct. Failure to obtain approval may result in cost disallowances.

C. FIXED RATES:

If a fixed rate is in this Agreement, it is based on an estimate of the costs for the period covered by the rate. When the actual costs for this period are determined, an adjustment will be made to a rate of a future year(s) to compensate for the difference between the costs used to establish the fixed rate and actual costs.

D. USE BY OTHER FEDERAL AGENCIES:

The rates in this Agreement were approved in accordance with the authority in Title 2 of the Code of Federal Regulations, Part 200 (2 CFR 200), and should be applied to grants, contracts and other agreements covered by 2 CFR 200, subject to any limitations in A above. The organization may provide copies of the Agreement to other Federal Agencies to give them early notification of the Agreement.

E. OTHER:

If any Federal contract, grant or other agreement is reimbursing facilities and administrative costs by a means other than the approved rate(s) in this Agreement, the organization should (1) credit such costs to the affected programs, and (2) apply the approved rate(s) to the appropriate base to identify the proper amount of facilities and administrative costs allocable to these programs.

BY THE INSTITUTION:

University of Alabama at Birmingham

(INSTITUTION)

Stephanie Mullins

(SIGNATURE)

Stephanie Mullins

(NAME)

UAB Chief Financial Officer | Associate VP for Financial Affairs

(TITLE)

9/29/17

(DATE)

ON BEHALF OF THE FEDERAL GOVERNMENT:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Darryl W. Mayes -S

Digitally signed by Darryl W. Mayes -S
DN: c=US, o=U.S. Government, ou=HHS, ou=PSC, ou=People, 0.9.2342.19200300.100.1.1=2000131569, cn=Darryl W. Mayes -S
Date: 2017.09.19 09:09:50 -04'00'

(SIGNATURE)

For Arif Karim

(NAME)

Director, Cost Allocation Services

(TITLE)

9/13/2017

(DATE) 6985

HHS REPRESENTATIVE: Shon Turner

Telephone: (214) 767-3261

SECTION II: SPECIAL REMARKS

TREATMENT OF FRINGE BENEFITS:

The fringe benefits are charged using the rate(s) listed in the Fringe Benefits Section of this Agreement. The fringe benefits included in the rate(s) are listed below.

TREATMENT OF PAID ABSENCES

Vacation, holiday, sick leave pay and other paid absences are included in salaries and wages and are claimed on grants, contracts and other agreements as part of the normal cost for salaries and wages. Separate claims are not made for the cost of these paid absences.

OFF-CAMPUS DEFINITION: For all activities performed in facilities not owned by the institution and to which rent is directly allocated to the project(s) the off-campus rate will apply. Grants or contracts will not be subject to more than one F&A cost rate. If more than 50% of a project is performed off-campus, the off-campus rate will apply to the entire project.

Equipment means article of nonexpendable, tangible personal property having a useful life of more than one year(s) and an acquisition cost of $5,000 or more per unit.

Fringe Benefits Include: FICA, Health & Life Insurance, Workers' Compensation, Salary Continuation, State Unemployment, Disability Insurance, Educational Assistance, Employee Training, EAP, Terminal Vacation Pay, Teacher's Retirement and TIAA/CREF, New Employee Orientation, Parental Leave, Benefit Focus, and Health EFX.

This agreement updates the Fringe Benefits Rates only.

The next Fringe Benefit rate proposal based on FYE 09/30/17 is due in our office by 03/31/18. The next Facilities and Administration rate proposal based on actual cost for FYE 09/30/2018 is due in our office by 03/31/2019.

Scope of Work – University of Alabama at Birmingham (UAB)

Drs. Muzny and Redden at UAB will serve as primary partners to co-PIs Drs. Klausner and Medina-Marino in providing vaginal microbiome expertise and statistical analysis expertise, respectively. Dr. Muzny will be responsible for all Aim 3 study-related activities including study design, study progress, data analysis, presentation of results at national and international conferences, manuscript preparation, and, along with Drs. Medina-Marino and Klausner, overseeing of all clinical work. She will assist in troubleshooting any difficulties that arise with the analysis and interpretation of the vaginal microbiome data collected in Aim 3. Dr. Redden will be the lead statistician on this proposal and will conduct the statistical analysis of all data collected in Aims 1-3.

To list Additional Location(s) for the Project/Performance Site Locations Component, use the format provided below. You can copy the informational table as many times as needed. Follow the instructions provided for Project/Performance Site Locations, indicating the Site Location number. You must enter the State and Country rather than selecting from a list. An asterisk (*) indicates required data.

Please delete these instructions before attaching this file to your Project/Performance Site Locations Component.

***Project Performance Site Location**	**Number: ___**
Organization Name	University of Alabama at Birmingham
DUNS Number	063690705
*Street1	1720 2nd Avenue South
Street2	ZRB 242
*City	Birmingham
County	Jefferson
*State or Province	Alabama
*Country	United States
*ZIP/Postal Code	35294-0009
*Project/Performance Site Congressional District	AL-007
*"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."	*Indicate Yes or No in response to the statement at left: _____No_____

To list Additional Senior/Key Person Profile(s) for the Senior/Key Person Profile(s) Component, use the format provided below. You can copy the informational table as many times as needed. Follow the instructions provided for Senior/Key Person [*n*] Profile, indicating the number of the profile. You must enter the Prefix, Suffix, State, Country, and Project Role, rather than selecting from a list. An asterisk (*) indicates required data. Attach a biographical sketch for each senior/key person separately.

Please delete these instructions before attaching this file to your Senior/Key Person Profile(s) Component.

***PROFILE – Senior/Key Person**	**Number: ___**
Prefix	
*First Name	Christina
Middle Name	A.
*Last Name	Muzny
Suffix	MD, MSPH
Position/Title	Associate Professor
Department	Department of Medicine
Organization Name	University of Alabama at Birmingham
Division	Infectious Diseases
*Street1	ZRB 242
Street2	1720 2nd Ave South
*City	Birmingham
County/Parish	Jefferson
*State or Province	Alabama
*Country	USA
*Zip/Postal Code	35233-0007
*Phone Number	205-975-3298
Fax Number	205-975-7764
*E-Mail	cmuzny@uabmc.edu
Credential, e.g., agency login	CMUZNY
*Project Role	Co-PI
Other Project Role Category	
Degree Type	MD
Degree Year	2003

To list Additional Senior/Key Person Profile(s) for the Senior/Key Person Profile(s) Component, use the format provided below. You can copy the informational table as many times as needed. Follow the instructions provided for Senior/Key Person [*n*] Profile, indicating the number of the profile. You must enter the Prefix, Suffix, State, Country, and Project Role, rather than selecting from a list. An asterisk (*) indicates required data. Attach a biographical sketch for each senior/key person separately.

Please delete these instructions before attaching this file to your Senior/Key Person Profile(s) Component.

***PROFILE – Senior/Key Person**	**Number: ___**
Prefix	
*First Name	David
Middle Name	T.
*Last Name	Redden
Suffix	PhD
Position/Title	Professor Public Health
Department	Biostatistics
Organization Name	University of Alabama at Birmingham
Division	Biostatistics
*Street1	RPHB 309D, zip 0022
Street2	1720 2nd Ave South
*City	Birmingham
County/Parish	Jefferson
*State or Province	Alabama
*Country	USA
*Zip/Postal Code	35233-0007
*Phone Number	205-975-9165
Fax Number	205-975-2540
*E-Mail	dredden@uab.edu
Credential, e.g., agency login	
*Project Role	Statistician
Other Project Role Category	
Degree Type	PhD
Degree Year	1995

Form Approved Through 10/31/2018 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
Clinical study of STI screening to prevent adverse birth and newborn outcomes

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)
Number: PA-19-055 Title: NIH Research Project Grant (Parent R01 Clinical Trial Required)

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Taylor, Christopher	PhD	CTay15

3c. POSITION TITLE
Associate Professor

3d. MAILING ADDRESS *(Street, city, state, zip code)*
533 Bolivar Street, 6th Floor
New Orleans, LA 70112-1393

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Microbiology, Immunology, and Parasitology

3f. MAJOR SUBDIVISION
Medicine

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 504-568-4065 FAX: 504-568-2918

E-MAIL ADDRESS:
CTay15@lsuhsc.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☒ No ☐ Yes	☐ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
	☐ No ☐ Yes	☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ No ☐ Yes — 5a. Animal Welfare Assurance No.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
09/01/2019	08/31/2024	$9,714	$14,280	$101,197	$148,761

9. APPLICANT ORGANIZATION
Name: Louisiana State University Health Sciences Ctr. – NO
Address: 433 Bolivar Street
New Orleans, LA 70112

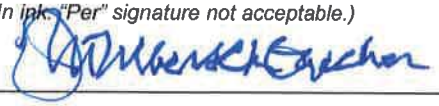
10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1-726087770-A2
DUNS NO. 782627814 Cong. District LA-002

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Nicole Hammill
Title: Assistant Director, Sponsored Projects
Address: 433 Bolivar Street, 6th Floor
New Orleans, LA 70112-2256
Tel: 504-568-4867 FAX: 504-568-6376
E-Mail: Spon_Proj@lsuhsc.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Joseph M. Moerschbaecher, III, PhD
Title: Vice Chancellor, Acad. Affairs
Address: 433 Bolivar Street, Suite 824
New Orleans, LA 70112-2256
Tel: 504-568-4804 FAX: 504-568-5588
E-Mail: ERA_SO_ACCT@lsuhsc.edu

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

SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*


DATE 1/24/19

LSU Health NEW ORLEANS

School of Medicine
Department of Microbiology, Immunology and Parasitology

Date: January 10, 2019

Application Title: Clinical Study of STI Screening to Prevent Adverse Birth and Newborn Outcomes

Proposed Project Period: September 1, 2019 – August 31, 2024
Proposed Budget: Year 1 Budget Request: $14,280; Project Budget Request: $148,761

On behalf of Louisiana State University Health Sciences Center - New Orleans (LSUHSC-NO) and the University of California, Los Angeles (UCLA), the undersigned are pleased to endorse the above referenced proposal.

This letter certifies that neither LSUHSC-NO nor UCLA is delinquent on any federal debt, nor is either institution presently debarred, proposed for debarment, declared ineligible or voluntarily excluded from covered transactions by a Federal department or agency.

This letter further certifies that both LSUHSC-NO and UCLA have valid Dun & Bradstreet (D&B) Universal Numbering System (DUNS) numbers.

Both LSUHSC-NO and UCLA certify that they are in compliance with 42 CFR Part 50.604 and currently maintain up-to-date, written, enforced policies on financial conflicts of interest (FCOIs). Each agrees to follow said policies throughout the life of any award. It is further certified that all study personnel have completed, or will complete prior to the expenditure of Public Health Service (PHS) funds (if applicable) the appropriate disclosures in accordance with their respective FCOI policies. Identified FCOIs will be made available to the grantee institution upon request.

The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the pertinent Federal regulations and policies and are prepared to negotiate written inter-organizational agreements that will ensure compliance with all such policies.

Louisiana State University Health Sciences Center - New Orleans
(Consortium Institution)

Chris Taylor 01/17/19
(Signature) (Date)
Christopher Taylor, PhD
Associate Professor
Dept. of Microbiology & Immunology

(Signature) (Date) 1/24/19
Joseph M. Moerschbaecher, III, PhD
Vice Chancellor, Academic Affairs

University of California, Los Angeles
(Grantee Institution)

(Signature) (Date)
Jeffrey D. Klausner, MD, MPH
Professor of Medicine
School of Public Health

(Signature) (Date)
Ms. Raellen Man
Director of Research Administration

University of California, Los Angeles

Office of Contract and Grant Administration

SUBRECIPIENT COMMITMENT FORM

All Subrecipients must complete this form when submitting a proposal to UCLA. It provides a checklist of documents and certifications required by sponsors and it must be endorsed by the authorized institutional representative prior to proposal submission.

Subrecipient's Legal Name: The Board of Supervisors of LSU and A&M College, herein represented by Louisiana State University Health Sciences Center – N.O.

Subrecipient's Principal Investigator: Christopher Taylor, PhD

UCLA's Principal Investigator: Drs. Klausner & Medine-Marino Prime Sponsor: NIH-NIDCR

UCLA's Proposal Title: Clinical study of STI screening to prevent adverse birth and newborn outcomes

Subrecipient Total Funds Requested: $148,761 Performance Period Begin Date: 09/01/2019 End Date: 08/31/2024

Section A: Proposal Documents – ALSO SEE SECTION E (pg.5); Answer the questions and if categorized as a Subrecipient continue to fill out the rest of the form.

The following documents are included in our subaward proposal submission and covered by the certifications below:

☒ STATEMENT OF WORK (Required)
☒ BUDGET AND BUDGET JUSTIFICATION (Required)
☒ SUBRECIPIENT COMMITMENT FORM (This form)

Section B: Certifications

1. **Facilities & Administrative Rates** included in this proposal have been calculated based on the following:
   - ☒ Our federally recognized negotiated F&A rates for this type of work. If this box is checked, a copy of your F&A rate agreement *must* be furnished to UCLA Office of Contract & Grant Administration (OCGA).
   - ☐ A reduced F&A rate dictated by the prime sponsor that we hereby agree to accept. Rate:_____ Base Type:_____
   - ☐ Not applicable (No indirect costs are requested by Subrecipient).

2. **Fringe Benefit Rates** included in this proposal have been calculated based on the following:
   - ☒ Rates are consistent with our Federally negotiated rates. If this box is checked, a copy of your Federal fringe benefit rate agreement *must* be furnished to UCLA OCGA.
   - ☐ Other rates as specified in Section F: Comments (please specify the basis on which the rate has been calculated)

3. **Human Subjects** YES ☐ NO ☒
   If **YES** copies of the following documentation must be provided before any subaward can be issued:
   1) IRB approval certification
   2) IRB approved project protocol
   3) Approved "Informed Consent" form
   4) Verification of IRB training
   5) Verification of FWA number and Expiration date

   Please forward these documents to UCLA's Principal Investigator as soon as they become available.
   If **YES** and NIH funding is involved:
   - Have all key personnel completed human subjects training at the subrecipient's institution? **YES** ☐ **NO** ☐
   - Please attach a list of key personnel who are on this project on a separate sheet.

4. **Animal Subjects** YES ☐ NO ☒
   If **YES**, a copy of the IACUC approval must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available.
   If **YES** and NIH funding is involved:
   Please provide your institution's PHS Assurance number. PHS Assurance No.: _____ Expiration Date: _____
   If you do not have one on file, you will need to apply for one and provide it to us before any subaward will be issued.

5. **Stem Cells** YES ☐ NO ☒
   If **YES**, a copy of the Stem Cell approval must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available.

6. **Dual Use Research of Concern (DURC)** (Applicable to projects funded by PHS/NIH)

☒ Not applicable.

Will this project use one or more of the following agents or toxins (Check all that apply)?

☐ Marburg virus	☐ Reconstructed 1918 Influenza virus	☐ Avian influenza virus (highly pathogenic)
☐ Variola minor virus	☐ Variola major virus	☐ Toxin-producing strains of Clostridium botulinum
☐ Rinderpest virus	☐ Yersinia pestis	☐ Bacillus anthracis
☐ Botulinum neurotoxin	☐ Francisella tularensis	☐ Foot-and-mouth disease virus
☐ Burkholderia mallei	☐ Burkholderia pseudomallei	☐ Ebola virus

If at least one box is checked, a copy of your Institution's Review Entity determination as to whether the research qualifies as DURC must be provided. Once we receive it, and it is determined by PHS/NIH that the research is in fact DURC; a copy of the mitigation plan must be provided to UCLA before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available. For more information, please see NIH Guide notice NOT-OD-15-017.

7. **Genomic Data Sharing Policy** (Applicable to projects funded by PHS/NIH, see announcement NOT-OD-14-124) **YES** ☐ **NO** ☒

If **YES**, a copy of the Institutional Certification for large-scale human genomic data must be provided before any subaward will be issued. Please forward these documents to UCLA's Principal Investigator as soon as they become available. Additionally, investigators are expected to make all large scale data (human and non-human) publicly available through a data repository (e.g. dbGaP, GEO, SRA).

8. **Cost Sharing** **YES** ☐ if **YES**, $_____ **NO** ☒

If **YES**, explanation of Cost Sharing sources *must* be included in the subrecipient's budget. Please note that an annual verification of cost share commitment will be required.

9. **National Science Foundation (NSF) Conflict of Interest**

Applicable to NSF, including NSF flow-through or any other program *except PHS/NIH* requiring Federal Financial disclosure.

☒ Not applicable because this project is not being funded by NSF or any other program requiring Federal Financial disclosure.

☒ Subrecipient organization/institution hereby certifies that it has an active and enforced policy on conflict of interest consistent with the provision of NSF Award & Administration Guide Chapter IV.A.

10. **Public Health Service (PHS) Financial Conflict of Interest**

Applicable to projects funded by PHS/NIH, or any other program requiring DHHS Financial Conflict of Interest (FCOI) disclosure.

☐ Not applicable because this project is not being funded by PHS/NIH or any other program requiring DHHS FCOI.

☒ Subrecipient organization/institution hereby certifies that it has an active and enforced policy on conflict of interest consistent with the provision of 42 CFR Part 50 Subpart F.

☐ My organization **DOES NOT HAVE** a PHS compliant policy in place but will have one at the time of award.
(A sample FDP FCOI policy can be found at http://sites.nationalacademies.org/PGA/fdp/PGA_061001).
List the names of individuals working on this project that is responsible for the design, conduct, or reporting of the research.
Each individual listed MUST fill out and attach the PHS Financial Disclosure form.

11. **National Science Foundation (NSF) Ethics in Research Training**

Applicable to projects funded by NSF or any other programs requiring Ethics in Research Training.

☒ Not applicable because this project is not being funded by NSF or any other programs requiring Ethics in Research Training.

☐ Subrecipient organization/institution hereby certifies that it will ensure that all undergraduates, graduate students, and postdoctoral researchers who will be supported by this NSF proposal will be trained on the oversight in the responsible and ethical conduct of research.

12. **Public Health Service (PHS) Research Misconduct**

Applicable to projects funded by PHS/NIH

☐ Not applicable because this project is not being funded by PHS/NIH.

☒ Subrecipient organization/institution hereby certifies that it has completed and submitted the "Assurance of Compliance by Sub-Award Recipients available at: http://ori.hhs.gov/sites/default/files/PHS-6315.pdf

13. **Certification of Debarment, Suspension, Proposed Debarment**

Is the Subrecipient Entity, Subrecipient PI, or any other employee or student participating in this project, debarred, suspended or otherwise excluded from or ineligible for participation in federal assistance programs or activities? **YES** ☐ **NO** ☒

If **YES**, please explain in Section F: Comments.

Subawards to any entity or individual include in the Federal Excluded Parties are prohibited.

If **NO**, the Organization Certifies they: (answer all questions below)

☐ are ☒ are not presently debarred, suspended, proposed for debarment, or declared ineligible for award of federal contracts

☐ are ☒ are not presently indicted for, or otherwise criminally or civilly charged by a government agency.

☐ have ☒ have not within three (3) years preceding this offer, been convicted of or had a civil judgment rendered against them for commission of fraud or criminal offense in connection with obtaining , attempting to obtain, or performing a public (federal, state, or local) contract or subcontract; violation of Federal or State antitrust statutes relating to the submission of offers, or commissions of contract or subcontract; violation of Federal or State antitrust statutes relating to the submission of offers, or commission of embezzlement, theft, forgery, bribery, falsification, or destruction of records, making false statements or receiving stolen property.

☐ have ☒ have not within 3 years preceding this offer, had one or more contracts terminated for default by any federal agency.

14. Subrecipient is what type of entity? Public/State Controlled Institution of Higher Education

Is the Subrecipient a for-profit entity? **YES** ☐ **NO** ☒

If **YES**, UCLA PI should complete the Fair and Reasonable Cost Analysis and attach it to this form.

Section C: Audit Status

1. Does the subrecipient receive an annual audit in accordance with OMB Circular A-133/Uniform Guidance? **YES** ☒ **NO** ☐

If **YES**,

a) A complete copy of subrecipient's most recent audit report, or the Internet URL link to a complete copy, must be furnished to UCLA OCGA before a subaward will be issued.

b) Has the audit been completed for the most recent fiscal year? **YES** ☒ **NO** ☐

c) Were there any audit findings reported? **YES** ☐ **NO** ☒

If **YES**, UCLA requires that the entity complete the Certificate of Compliance

If **NO**, UCLA requires that the entity complete a Financial Audit Management Questionnaire and may require a limited-scope audit before a subaward can be issued.

Section D: Subrecipient Institutional Information

1. Location of Subrecipient

Address: 433 Bolivar Street

City, State, Zip: New Orleans, LA 70112 Congressional District: LA-002

Primary Place of Performance *(If primary place of performance is different than Location of Subrecipient)*

Address: 533 Bolivar Street, 6th Floor

City, State, Zip: New Orleans, LA 70112 Congressional District: LA-002

2. Subrecipient DUNS Number: 782627814

3. Subrecipient EIN Number: 1-726087770-A2

4. Subrecipient NAICS Code: 611310 - Colleges, Universities, and Professional Schools

5. Is Subrecipient owned or controlled by a parent entity? **YES** ☐ **NO** ☒ If **YES**, provide information for the parent entity below:

Address: _____

City, State, Zip: _____ Congressional District: _____

Parent DUNS Number: _____

Parent EIN Number: _____

6. Is subrecipient currently registered in System for Award Management (SAM)? (www.sam.gov) **YES** ☒ **NO** ☐
If **NO**, organizations that have not registered with SAM will need to obtain a DUNS number first and then access the online registration through the SAM (System for Award Management) home page at https://www.sam.gov (U.S. organizations will also need to provide an Employer Identification Number from the Internal Revenue Service that may take an additional 2-5 weeks to become active). Completing and submitting the registration takes approximately one hour to complete and your SAM registration will take 3-5 business days to process. **Subrecipient *must have* a current SAM registration and maintain their current information in SAM prior to issuance of a Subaward.**

7. Is the Subrecipient's Principal Investigator and/or any other Investigator (key personnel) on the proposed subaward a UCLA student (undergraduate or graduate), postdoctoral scholar, or other trainee, or a faculty or staff employee? **YES** ☐ **NO** ☒
If **YES,** please describe the relationship in Section F: Comments and notify the OCGA Subaward Team at ocgasubawards@em.ucla.edu.

8. Federal Funding and Accountability Transparency Act (FFATA)
Provide the names and total compensation of the five (5) most highly compensated officers of the subrecipient entity if:
   a. The recipient in its preceding fiscal year received:
      i. 80 percent or more of its annual gross revenues in Federal awards; **AND**
      ii. $25,000,000 or more in annual revenues from the Federal awards; **AND**
   b. The public does NOT have access to information about the compensation of the senior executives of the entity through periodic reports filed under section 13(a) or 15(d) of the Securities and Exchange Act of 1934 (15 U.S. C. 78m(a), 78o(d) or section 6104 of the Internal Revenue Service Code of 1986 [26 USC 6104]

If **YES** to a and b: Attach List
If **NO** to a and/or b: Check this box ☒
Note: "Total compensation" means the cash and noncash dollar value earned by the executive during the subrecipient's past fiscal year of the following (for more information see 17 CFR 229.402 (c)(2)).

1) Salary and Bonus
2) Award of stock, stock options, and stock appreciation rights. Use the dollar amount recognized for financial statement reporting purposes with respect to the fiscal year in accordance with FAS 123R
3) Earnings for services under non-equity incentive plans. Does not include group life, health, hospitalization, or medical reimbursement plans that do not discriminate in favor of executives, and are available generally to all salaried employees.
4) Change in pension value. This is the change in present value of defined benefit and actuarial pension plans.
5) Above-market earning of deferred compensation which are not tax-qualified
6) Other compensation. For Example, severance, termination payments, value of life insurance paid on behalf of the employee, perquisites or property if the values for the executive exceed $10,000

Project Description: In compliance with FFATA reporting obligations, please provide a succinct description of the overall purpose and expected outcomes. This information will be displayed on the https://www.USAspending.gov website and will be available to the general public.

Dr. Christopher Taylor, Associate Professor at Louisiana State University Health Sciences Center - NO, is an expert in the field of microbiome visualization and analysis and has a specific research focus on the vaginal microbiome with relation to studies of STIs and chlamydia treatment. LSUHSC will collaborate with UCLA on the analysis and visualization of the vaginal microbiome data during years 4 and 5, and will provide consultation during years 1, 2, and 3 on data collection and processing for the vaginal microbiome aim. During years 4 and 5, Dr. Taylor will utilize his computational resources, open source microbiome analysis software, and custom scripts and software developed in the Taylor lab for processing and analysis of the vaginal microbiome data. He will work with the other investigators on data visualization and preparation of manuscripts.

Section E: Subrecipient Requirements and Responsibilities

Before submitting a subaward proposal, the subrecipient must verify that it fits the characteristics of a subrecipient, rather than those of a contractor. The following chart outlines the differences. Please check all that apply.

Subrecipient	Contractor
☒ Performance represents an intellectually significant portion of the overall programmatic effort and is measured against the objectives of the Federal program	☐ Provides goods or services that are ancillary to the operation of the Federal program
☒ Will use the Federal funds to carry out a program for a public purpose, as opposed to providing goods or services for the benefit of UCLA	☐ Provides the goods or services purchased with the Federal funds within normal business operations
☒ Is responsible for adhering to applicable Federal program requirements specified in the Federal award	☐ Provides similar goods or services to many different purchasers
☒ There is an identified principal investigator for the subrecipient who has responsibility for making programmatic decisions	☐ Is not subject to the compliance requirements of the Federal program as a result of the agreement with UCLA
	☐ Normally operates in a competitive environment

☒ **YES** ☐ **NO** My organization is properly categorized as a subrecipient as described above.

If "No," please contact the UCLA PI about procuring your organization's products and services as a contractor.

Section F: Comments (please attach additional pages if necessary)

Approved for Subrecipient

The information, certifications, and representations above have been read, signed, and made by an authorized institutional representative of the Subrecipient named herein. The appropriate programmatic and administrative personnel involved in this application are aware of agency policies in regard to subawards and are prepared to establish the necessary inter-institutional agreements consistent with those policies. Any work begun and/or expenses incurred prior to execution of a subaward agreement are at the Subrecipient's own risk.

Signature of Subrecipient's Authorized Institutional Representative

Joseph M. Moerschbaecher, III, PhD
Typed Name of Subrecipient's Authorized Institutional Representative

Vice Chancellor, Acad. Affairs
Title of Subrecipient's Authorized Institutional Representative

1/24/19
Date

433 Bolivar Street, Suite 824
Street Address

New Orleans, LA 70112
City, State, Zip

504-568-4804
Phone

504-568-5588
Fax

ERA_SO_ACCT@lsuhsc.edu
Email Address

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

ASSURANCE OF COMPLIANCE BY SUB-AWARD RECIPIENTS

Regarding Procedures for Dealing With and Reporting Research Misconduct Allegations

FORM APPROVED: OMB No. 0937-0198; Expires: 05/31/2020
See Statement of Burden Below

INSTITUTIONAL OFFICIAL'S NAME
Joseph M. Moerschbaecher, III, PhD

INSTITUTIONAL OFFICIAL'S TITLE
Vice Chancellor, Acad. Affairs

Please make any mailing changes in the space to the right:

Place mailing label here.

NAME OF INSTITUTION
The Board of Supervisors of LSU and A&M College, herein represented Louisiana State University Health Sci. Center-NO

MAILING ADDRESS OF INSTITUTIONAL OFFICIAL
433 Bolivar Street, Room 824
New Orleans, LA 70112-2256

NAME OF INSTITUTION FROM WHICH PHS FUNDS ARE RECEIVED AS SUBRECIPIENT
University of California, Los Angeles

Section I. ORI Assurance of Compliance for Sub-Award recipients

Institutions with U.S. Public Health Service (PHS) supported biomedical or behavioral research, research training or activities related to that research or research training must provide PHS with an assurance of compliance with the Public Health Service Policies on Research Misconduct, 42 C.F.R. Part 93.

Section II. Certification

I certify that:

(a) This institution has written policies and procedures in compliance with 42 C.F.R. Part 93 for inquiring into and investigating allegations of research misconduct; and

(b) This institution is in compliance with its own policies and procedures and the requirements of 42 C.F.R. Part 93.

(c) The person responsible for administering the institutions procedures, compliant with 42 CFR 93.300(b) is? (At some Institutions this person is called the Research Integrity Officer or RIO).

Name of Official: Joseph M. Moerschbaecher, III, PhD Title: Vice Chancellor, Acad. Affairs

(d) The person responsible for "fostering a research environment that promotes the responsible conduct of research" in compliance with 42 CFR 93.300(c) is? At some institutions this person is called the RCR coordinator or administrator.

Name of Official: Joseph M. Moerschbaecher, III, PhD Title: Vice Chancellor, Acad. Affairs

Official Certifying for Institution

NAME OF OFFICIAL *(Please type)*	TITLE
Joseph M. Moerschbaecher, III, PhD	Vice Chancellor, Acad. Affairs
SIGNATURE 	DATE 1/24/19
TELEPHONE NUMBER (504) 568-4804	FAX NUMBER (504) 568-5588

E-MAIL ADDRESS OF OFFICIAL: ERA_SO_ACCT@lsuhsc.edu

STATEMENT OF BURDEN

Public reporting burden for this collection of information is estimated to average 5 minutes to complete the form, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: OS Reports Clearance Officer, Hubert H. Humphrey Building, Room 503-H, 200 Independence Avenue, S.W., Washington, D.C. 20201 (Attn: PRA) and to: Office of Management and Budget, Paperwork Reduction Project (0937-0198) Washington, D.C. 20502. *Please do not return this form to either of these addresses.*

RETURN THIS FORM TO:

Assurance Program
Office of Research Integrity
1101 Wootton Parkway, Suite 750
Rockville, MD 20852

Phone: (240) 453-8407
FAX: (301) 594-0039
E-Mail: Robin.Parker@hhs.gov

Institutional Assurances and Certifications

Status

The Office of Research and Integrity Certification Status is: **Assurance OK**

This certification expires on: **04/30/2019**

Assurances and Certifications

This institution complies with all laws, policies and regulations prohibiting discrimination based on:

- 02/28/2007 Age Discrimination Assurance
- 02/28/2007 Civil Rights Assurance
- 02/28/2007 Handicapped Individuals Assurance
- 02/28/2007 Inclusion of Children Policy
- 02/28/2007 Sex Discrimination Assurance
- 02/28/2007 Women and Minority Inclusion Policy

This institution complies with all laws and regulations regarding:

- 08/11/2008 ClinicalTrials.gov Requirement
- 02/28/2007 Conflict of Interest Assurance
- 02/28/2007 Delinquent Debt Assurance
- 02/28/2007 Drugfree Workplace Assurance
- 08/11/2008 Impact of Grant Activities on the Environment and Historic Properties
- 02/28/2007 Institutional Debarment Assurance
- 02/28/2007 Lobbying Assurance
- 10/27/2009 Smoke-Free Workplace

Research at this institution meets all requirements for:

- 10/27/2009 Graduate Student Training for Doctoral Degrees (D43, TU2, T15, T32, T37, T90, U2R, U90, and U54/TL1 only)
- 02/28/2007 Human Subjects
- 05/08/2007 PI Assurance
- 05/08/2007 Prohibited Research
- 02/28/2007 Recombinant DNA and Human Gene Transfer
- 02/28/2007 Research Misconduct
- 02/28/2007 Research With Human Embryonic Stem Cells
- 05/08/2007 Select Agent Research
- 02/28/2007 Transplantation of Human Fetal Tissue
- 02/28/2007 Vertebrate Animals

COLLEGES AND UNIVERSITIES RATE AGREEMENT

EIN: 1726087770A2

ORGANIZATION:

LSU Health Sciences Center, New Orleans
433 Bolivar Street
Suite 811
New Orleans, LA 70112-2223

DATE:04/30/2018

FILING REF.: The preceding agreement was dated 05/25/2017

The rates approved in this agreement are for use on grants, contracts and other agreements with the Federal Government, subject to the conditions in Section III.

SECTION I: INDIRECT COST RATES

RATE TYPES: FIXED FINAL PROV. (PROVISIONAL) PRED. (PREDETERMINED)

	EFFECTIVE PERIOD				
TYPE	FROM	TO	RATE(%)	LOCATION	APPLICABLE TO
PRED.	07/01/2017	06/30/2018	46.00	On Campus	Organized Research
PRED.	07/01/2018	06/30/2021	47.00	On Campus	Organized Research
PRED.	07/01/2017	06/30/2021	46.00	On Campus	Instruction
PRED.	07/01/2017	06/30/2021	43.50	On Campus	Other Sponsored Activities
PRED.	07/01/2017	06/30/2021	26.00	Off Campus	All Programs
PROV.	07/01/2021	Until Amended			Use same rates and conditions as those cited for fiscal year ending June 30, 2021.

*BASE

Modified total direct costs, consisting of all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel and up to the first $25,000 of each subaward (regardless of the period of performance of the subawards under the award). Modified total direct costs shall exclude equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and fellowships, participant support costs and the portion of each subaward in excess of $25,000. Other items may only be excluded when necessary to avoid a serious inequity in the distribution of indirect costs, and with the approval of the cognizant agency for indirect costs.

ORGANIZATION: LSU Health Sciences Center, New Orleans
AGREEMENT DATE: 4/30/2018

SECTION I: FRINGE BENEFIT RATES**

TYPE	FROM	TO	RATE(%)	LOCATION	APPLICABLE TO
FIXED	7/1/2017	6/30/2018	45.00	All	F/T Faculty & Staff
FIXED	7/1/2018	6/30/2019	43.00	All	F/T Faculty & Staff
PROV.	7/1/2019	6/30/2021			Use same rates and conditions as those cited for fiscal year ending June 30, 2019.

** DESCRIPTION OF FRINGE BENEFITS RATE BASE:
Salaries and wages.

SECTION II: SPECIAL REMARKS

TREATMENT OF FRINGE BENEFITS:

The fringe benefits are charged using the rate(s) listed in the Fringe Benefits Section of this Agreement. The fringe benefits included in the rate(s) are listed below.

TREATMENT OF PAID ABSENCES

Vacation, holiday, sick leave pay and other paid absences are included in salaries and wages and are claimed on grants, contracts and other agreements as part of the normal cost for salaries and wages. Separate claims are not made for the cost of these paid absences.

OFF-CAMPUS DEFINITION: For all activities performed in facilities not owned by the institution and to which rent is directly allocated to the project(s) the off-campus rate will apply. Grants or contracts will not be subject to more than one F&A cost rate. If more than 50% of a project is performed off-campus, the off-campus rate will apply to the entire project.

FRINGE BENEFITS:

Retirement
Unemployment Insurance
Health Insurance
Terminal Leave
Sabbatical Leave
Unfunded Retirement
Worker's Compensation
FICA
Life Insurance
Stipends

Your next fringe benefit proposal, based on actual costs for the fiscal year ending 06/30/18, is due in our office by 12/31/18.

Your next facilities and administrative proposal, based on actual costs for the fiscal year ending 06/30/20, is due in our office by 12/31/20.

Equipment means tangible personal property (including information technology systems) having a useful life of more than one year and a per-unit acquisition cost which equals or exceeds the lesser of the capitalization level established by the non-Federal entity for financial statement purposes, or $5,000.

SECTION III: GENERAL

A. LIMITATIONS:

The rates in this Agreement are subject to any statutory or administrative limitations and apply to a given grant, contract or other agreement only to the extent that funds are available. Acceptance of the rates is subject to the following conditions: (1) Only costs incurred by the organization were included in its facilities and administrative cost pools as finally accepted: such costs are legal obligations of the organization and are allowable under the governing cost principles; (2) The same costs that have been treated as facilities and administrative costs are not claimed as direct costs; (3) Similar types of costs have been accorded consistent accounting treatment; and (4) The information provided by the organization which was used to establish the rates is not later found to be materially incomplete or inaccurate by the Federal Government. In such situations the rate(s) would be subject to renegotiation at the discretion of the Federal Government.

B. ACCOUNTING CHANGES:

This Agreement is based on the accounting system purported by the organization to be in effect during the Agreement period. Changes to the method of accounting for costs which affect the amount of reimbursement resulting from the use of this Agreement require prior approval of the authorized representative of the cognizant agency. Such changes include, but are not limited to, changes in the charging of a particular type of cost from facilities and administrative to direct. Failure to obtain approval may result in cost disallowances.

C. FIXED RATES:

If a fixed rate is in this Agreement, it is based on an estimate of the costs for the period covered by the rate. When the actual costs for this period are determined, an adjustment will be made to a rate of a future year(s) to compensate for the difference between the costs used to establish the fixed rate and actual costs.

D. USE BY OTHER FEDERAL AGENCIES:

The rates in this Agreement were approved in accordance with the authority in Title 2 of the Code of Federal Regulations, Part 200 (2 CFR 200), and should be applied to grants, contracts and other agreements covered by 2 CFR 200, subject to any limitations in A above. The organization may provide copies of the Agreement to other Federal Agencies to give them early notification of the Agreement.

E. OTHER:

If any Federal contract, grant or other agreement is reimbursing facilities and administrative costs by a means other than the approved rate(s) in this Agreement, the organization should (1) credit such costs to the affected programs, and (2) apply the approved rate(s) to the appropriate base to identify the proper amount of facilities and administrative costs allocable to these programs.

BY THE INSTITUTION:

LSU Health Sciences Center, New Orleans

(INSTITUTION)

(SIGNATURE)

Ronnie Rodriguez, CPA

(NAME)

Director of Accounting Services

(TITLE)

May 9, 2018

(DATE)

ON BEHALF OF THE FEDERAL GOVERNMENT:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

(AGENCY)

Arif M. Karim -S Digitally signed by Arif M. Karim -S DN: c=US, o=U.S. Government, ou=HHS, ou=PSC, ou=People, cn=Arif M. Karim -S, 0.9.2342.19200300.100.1.1=20002128... Date: 2018.05.09 09:57:09 -05'00'

(SIGNATURE)

Arif Karim

(NAME)

Director, Cost Allocation Services

(TITLE)

4/30/2018

(DATE) 4136

HHS REPRESENTATIVE: Theodore Foster

Telephone: (214) 767-3261

DEPARTMENT OF HEALTH & HUMAN SERVICES

Program Support Center
Financial Management Portfolio
Cost Allocation Services

1301 Young Street, Room 732
Dallas, TX 75202
PHONE: (214) 767-3261
FAX: (214) 767-3264
EMAIL: CAS-Dallas@psc.hhs.gov

April 30, 2018

Mr. Ronnie Rodriguez, CPA
Director of Accounting Services
Louisiana State University Health Sciences Center – New Orleans
433 Bolivar Street
New Orleans, LA 70112-2223

Dear Mr. Rodriguez:

A copy of a facilities and administrative (F&A) cost and fringe benefit (FB) Rate Agreement are being sent to you for your signature. This Agreement reflects an understanding reached between your organization and a member of my staff concerning F&A and FB rates that may be used to support your claim for these indirect costs on grants and contracts with the Federal Government.

Please have the Agreement signed by an authorized representative of your organization and return it to me by email, retaining the copy for your files. Our email address is CAS-Dallas@psc.hhs.gov. We will reproduce and distribute the Agreement to the appropriate awarding organizations of the Federal Government for their use.

The Office of Management and Budget (OMB) has requested that we reach an agreement with each institution on components for the published F&A cost rates. The attached form(s) are provided for that purpose. Please sign the form(s) and return them with an agreement.

During our review of your proposal, it was disclosed that the Institution's actuarially determined pension contributions exceeded the Governmental Accounting Standards Board (GASB) Statement No. 68 calculated pension expense. However, 2 CFR 200.431(g)(3) only allows pension plan costs determined in accordance with GAAP (i.e., GASB 68). The Office of Management and Budget (OMB) is aware of this issue and is currently considering revising the regulations. Therefore, we reserve the right to revise this Agreement to disallow the pension contributions in excess of the GASB 68 calculated pension expense, if OMB does not revise the regulation or issue an exception.

In addition, your FB cost rate(s) for the fiscal year ending June 30, 2018 based on actual costs for the fiscal year ended June 30, 2016 and FB cost rates for the fiscal year ending June 30, 2019 based on actual costs for the fiscal year ended June 30, 2017 under-recovered (-) or over-recovered (+) amounts are listed below:

	2016/2018	2017/2019
F/T Faculty & Staff:	($4,012,571)	$116,029

The fixed rate(s) for the fiscal years ended June 30, 2016 and June 30, 2017 are considered final.

A Fringe Benefit cost proposal, together with supporting information and the certified audit financial statement, is required each year. Thus, your next Fringe Benefit cost proposal based on actual costs for the fiscal year ending June 30, 2018 is due in our office by December 31, 2018. Your next Facilities and Administrative cost rate proposal based on actual costs for the fiscal year ending June 30, 2020 is due in our office by December 31, 2020.

Since this is an integral part of the negotiation agreement, please note your acceptance by signing in the space provided below of this letter.

Thank you for your cooperation.

Sincerely,

Arif M. Karim -S

Digitally signed by Arif M. Karim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=PSC, ou=People, cn=Arif M. Karim -S, 0.9.2342.19200300.100.1.1=2000212895
Date: 2018.05.09 09:58:54 -05'00'

Arif Karim
Director
Cost Allocation Services

Enclosures

ACCEPTANCE

LSU HSC – New Orleans
Institution

Signature

Ronnie Rodriguez, CPA
Name

Director of Accounting Services
Title

May 9, 2018
Date