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 HD084274

b. Agency Routing Identifier

c. Previous Grants.gov Tracking ID

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

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

Department: Division:

Street1: Office of Contract and Grant Administration Street2: 11000 Kinross Avenue, Suite 211

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:
Miss	Yessenia		Sarmiento	

Position/Title: Senior Grant Analyst

Street1: UCLA Office of Contract & Grant Adm Street2: 11000 Kinross Avenue, Suite 211

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

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

Phone Number: 310-794-0393 Fax Number: Email: yessenia.sarmiento@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:

Pilot Study of STI Screening and Treatment for PMTCT

12. PROPOSED PROJECT:

Start Date	Ending Date
09/01/2015	08/31/2017

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
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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	$354,087.00
b. Total Non-Federal Funds	$0.00
c. Total Federal & Non-Federal Funds	$354,087.00
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:
Ms.	Catherine		Rujanuruks	

Position/Title: Departmental Research Assoc.
Organization Name: Regents of the University of California, Los Angeles
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Email: domdra@mednet.ucla.edu

Signature of Authorized Representative **Date Signed**

20. Pre-application File Name: Mime Type:

21. Cover Letter Attachment File Name: cover_letter1033654098.pdf Mime Type: application/pdf

UNIVERSITY OF CALIFORNIA, LOS ANGELES

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Public Health
Division of Infectious Diseases and Program in Global Health
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April 13, 2015

Bryan S. Clark, M.B.A.
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
31 Center Drive
Building 31, Room 2A32
Bethesda, MD 20892-2425

RE: PA-13-303 (R21) Grant #HD084274

Dear Mr. Clark:

Dr. Andrew Medina-Marino and I are very pleased to resubmit this application for our study, entitled "***Pilot Study of STI Screening and Treatment for PMTCT.***" We resubmit this proposal for your consideration as an R21. We believe this application to be innovative and extremely significant to maternal-child health, and were encouraged by the strong, positive reviews the proposal received in its first review.

Within NICHD, we think this may be a good fit for review by the Population Sciences or Obstetrics and Maternal-Fetal Biology Study Groups.

In addition, given the direct relevance of the proposal to the prevention of HIV transmission from HIV-infected mothers-to-children and HIV prevention, if deemed of high interest, this proposal should be considered for funding by NIAID, DAIDS. We would request NIAID/DAIDS be added as a second institute.

This proposal brings together laboratory and public health experts from the UCLA Program in Global Health in the United States and the Foundation for Professional Development (FPD) in South Africa, to analyze the impact of screening HIV-infected pregnant women for NG and CT on longitudinal birth and infant outcomes, especially the prevention of mother-to-child transmission of HIV.

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

Thank you.

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

Project/Performance Site Location(s)

Project/Performance Site Primary Location

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

* Street1: 10833 Le Conte Ave.		Street2: CHS 13-154
* City: Los Angeles	County: Los Angeles	* State: CA: California
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: 90095-1725
DUNS Number: 092530369	* Project/Performance Site Congressional District: CA-033	

Project/Performance Site Location 1

Organization Name: Foundation for Professional Development (Pty) Ltd

* Street1: Struland Office Park, 173 Mary Road		Street2: The Willows
* City: Pretoria 0184	County:	* State:
Province:	* Country: ZAF: SOUTH AFRICA	* Zip / Postal Code:
DUNS Number: 568904572	* Project/Performance Site Congressional District: 00-000	

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

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_abstract1033653747.pdf	Mime Type: application/pdf
8. Project Narrative	project_narrative1033653749.pdf	Mime Type: application/pdf
9. Bibliography & References Cited	Literature_Cited1033653748.pdf	Mime Type: application/pdf
10. Facilities & Other Resources	facilities_and_resources1033653850.pdf	Mime Type: application/pdf
11. Equipment	equipment1033653750.pdf	Mime Type: application/pdf

PROJECT ABSTRACT

The proposed study will help fill critical gaps in the understanding of how bacterial STIs may impact mother-to-child-transmission (MTCT) of HIV infection and infant morbidity and mortality in the era of combination antiretroviral therapy in pregnant women. We propose a study to investigate screening for *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) infections, and the potential impact of a screening program on the MTCT of HIV infection. Recent research by our group, including in South Africa, has demonstrated that NG and CT infections doubled the risk of mother-to-child HIV transmission.

South Africa's estimated preterm delivery rate of 8 per 100 live-births results in more than 80,000 preterm births annually, associated with about 60% infant mortality. With one of the largest numbers of HIV-infected pregnant women delivering annually in the world (>300,000), both adverse birth outcomes and HIV MTCT are significant public health problems; despite this, few studies have systematically measured the role of STIs and adverse birth outcomes in HIV-infected South African women.

There are two specific aims to our proposal. **Aim 1**: We will determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit, in order to: a) determine the proportion of eligible women consenting to testing (acceptability) and NG/CT-infected women receiving treatment within two weeks of specimen collection (feasibility), b) estimate the prevalence of CT and NG in HIV-infected pregnant women in Tshwane District, South Africa; and c) examine correlates of CT and/or NG infection and CT/NG treatment outcomes among pregnant women in the study. **Aim 2**: We will describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG, in order to: a) estimate the frequency of adverse birth outcomes and their association with CT and NG screening and treatment; and b) estimate the frequency of HIV MTCT and its association with CT and NG screening and treatment.

This pilot study is designed to determine the feasibility and acceptability of routinizing CT/NG screening and treatment of HIV-infected pregnant women, including treatment of partners to prevent re-infection. It has the potential to significantly inform programs aimed at the prevention of HIV MTCT in South Africa and to directly impact clinical and public health practices in low and middle-income countries relating to maternal-child health, especially relating to bacterial STIs.

RELEVANCE TO PUBLIC HEALTH

This pilot study will enhance knowledge of the prevalence of maternal and congenital infections and birth outcomes in high risk populations in low and middle-income countries, and explore how gonorrhea and chlamydia may influence mother-to-child transmission (MTCT) of HIV. It has the potential to significantly inform programs aimed at the prevention of HIV MTCT in South Africa and to directly impact clinical and public health practices in low and middle-income countries relating to maternal-child health, especially relating to bacterial STIs.

LITERATURE CITED

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FACILITIES AND OTHER RESOURCES
Scientific Environment

The proposed research will be conducted within the University of California, Los Angeles (UCLA) and the Foundation for Professional Development (FPD), and will benefit enormously from the institutional support for global health research in those two entities, and the 5 year collaborative relationship between UCLA and South Africa, specifically maintained by Dr. Jeffrey Klausner of the UCLA/Program in Global Health and Dr. Andrew Medina-Marino of FPD. The benefit of the UCLA/FPD collaboration to this research is invaluable.

University of California, Los Angeles (UCLA)

Division of Infectious Diseases, Program in Global Health

After living in South Africa from 2009-2011 leading the CDC PEPFAR HIV Program, Jeffrey D. Klausner, MD, MPH, was recruited to UCLA in Fall 2011 and joined the Program in Global Health within the Division of Infectious Diseases, Department of Medicine. The Unit has a broad and growing portfolio of prevention, clinical and policy research, focused primarily on HIV and developing country issues. In addition to ongoing NIH-funded research projects in South Africa, Botswana, Haiti, Malawi, Peru, and China, the UCLA PGH maintains satellite offices in South Africa, Peru and Malawi. From 2009-2011 Dr. Klausner resided in Pretoria, South Africa, home of FPD and worked weekly as a clinician in the Pretoria primary healthcare system.

Office Space:
The UCLA Program in Global Health has a designated office space in the Community Health Sciences Building, located on the UCLA campus. For this project, we will create a field office for study staff.

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:
Mr. Greg Szekeres is the IRB Coordinator and Else Henry is the Business Manager for the Program in Global Health. She is supported by the administrative team, including Project Assistant Kristine Mariscal, 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)

The Foundation for Professional Development was established in 1997 by the South African Medical Association (SAMA). In 2000, FPD became registered as a private company. FPD prides itself on being one of a few private higher education institutions 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.

Laboratory: Both FPD clinics – KY Motubatse and Soshanguve Community Health Centre – do not have on-site microbiology laboratories; one benefit of the Xpert® CT/NG assay is that it can be run appropriately in community clinics and does not require location in an advanced laboratory. Both clinics have dedicated antenatal blocks which have a "laboratory area" where the machine will be located. These areas are well-lit, cleaned daily, and access is tightly controlled for privacy and security reasons. Both clinics already regularly perform testing on the Gene Xpert® MTB/RIF, also by Cepheid.

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.

EQUIPMENT

The only major item of equipment relevant to this proposal is the Xpert® testing equipment, which will be loaned to the two study clinics by Cepheid at no cost for use in this pilot study. All 600 tests for gonorrhea and chlamydia that will be conducted as part of Aim 2 will be conducted via the Xpert® CT/NG assay. This on-demand testing system delivers same-day results within 90 minutes, and requires minimal training and skill for accurate use. The specimen will be self-collected by participants in the clinic using individual Xpert CT/NG Vaginal/Endocervical Specimen Collection kits. The sample will then be transferred by clinic staff to an Xpert CT/NG test cartridge, and the cartridge inserted into the Xpert CT/NG machine to begin the automated testing (see below).

The Xpert assay machines will be loaned by Cepheid, and 600 specimen collection kits and test cartridges will be donated (see Letter of Support). Testing equipment will be stored in the laboratory area of the antenatal block of each study clinic (see Facilities and Resources page for more information on those testing areas) and training for study staff who will be using the equipment will be collaboratively offered by FPD and Cepheid.

No other equipment will be used in the course of this pilot study.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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

Position/Title: Professor
Department: Medicine

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

* Street1: 10833 Le Conte Ave.
Street2: CHS 13-154

* City: Los Angeles
County: Los Angeles County
* State: CA: California
Province:

* Country: USA: UNITED STATES
* Zip / Postal Code: 90095-1725

*Phone Number	Fax Number	* E-Mail
310-267-0409	310-825-3157	JDKlausner@mednet.ucla.edu

Credential, e.g., agency login: jklausner

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

Degree Type:
Degree Year:

	File Name	Mime Type
***Attach Biographical Sketch**	Biosketch_Klausner1033654337.pdf	application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix
Dr.	Andrew	G.A	Medina-Marino	Ph.D.

Position/Title: Head of Research
Department:

Organization Name: Foundation for Professional Development (Pty) Ltd
Division:

* Street1: Struland Office Park, 173 Mary Road
Street2: The Willows

* City: Pretoria 0184
County:
* State:
Province:

* Country: ZAF: SOUTH AFRICA
* Zip / Postal Code:

*Phone Number	Fax Number	* E-Mail
+27 12 816 9253		andrewm@foundation.co.za

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

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

Degree Type:
Degree Year:

	File Name	Mime Type
***Attach Biographical Sketch**	Bios-ketch_Medina_Marino1033653759.pdf	application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix
Ms.	Joy	Ikechi	Ebonwu	MPH

Position/Title: Epidemiologist
Department:

Organization Name: Foundation for Professional Development (Pty) Ltd | Division:

* Street1: Struland Office Park, 173 Mary Road | Street2: The Willows

* City: Pretoria 0184 | County: | * State: | Province:

* Country: ZAF: SOUTH AFRICA | * Zip / Postal Code:

*Phone Number	Fax Number	* E-Mail
27 12 816 9037		joye@foundation.co.za

Credential, e.g., agency login:

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

Degree Type:
Degree Year:

	File Name	Mime Type
***Attach Biographical Sketch**	Biosketch_Ebonwu1033653762.pdf	application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix
Dr.	Xiaoyan		Wang	PhD

Position/Title: Adjunct Assistant Professor | Department: Medicine

Organization Name: UCLA David Geffen School of Medicine | Division: GIM/HSR

* Street1: 911 Broxton Ave | Street2: 1st Floor

* City: Los Angeles | County: Los Angeles County | * State: CA: California | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 90024-2801

*Phone Number	Fax Number	* E-Mail
310-794-3114		xywang@mednet.ucla.edu

Credential, e.g., agency login: WANGXY2

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

Degree Type:
Degree Year:

	File Name	Mime Type
***Attach Biographical Sketch**	Biosketch_Wang1033653851.pdf	application/pdf
Attach Current & Pending Support		

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

Additional Senior/Key Person Form Attachments

When submitting senior/key persons in excess of 8 individuals, please attach additional senior/key person forms here. Each additional form attached here, will provide you with the ability to identify another 8 individuals, up to a maximum of 4 attachments (32 people).

The means to obtain a supplementary form is provided here on this form, by the button below. In order to extract, fill, and attach each additional form, simply follow these steps:

- Select the "Select to Extract the R&R Additional Senior/Key Person Form" button, which appears below.
- Save the file using a descriptive name, that will help you remember the content of the supplemental form that you are creating. When assigning a name to the file, please remember to give it the extension ".xfd" (for example, "My_Senior_Key.xfd"). If you do not name your file with the ".xfd" extension you will be unable to open it later, using your PureEdge viewer software.
- Using the "Open Form" tool on your PureEdge viewer, open the new form that you have just saved.
- Enter your additional Senior/Key Person information in this supplemental form. It is essentially the same as the Senior/Key person form that you see in the main body of your application.
- When you have completed entering information in the supplemental form, save it and close it.
- Return to this "Additional Senior/Key Person Form Attachments" page.
- Attach the saved supplemental form, that you just filled in, to one of the blocks provided on this "attachments" form.

Important: Please attach additional Senior/Key Person forms, using the blocks below. Please remember that the files you attach must be Senior/Key Person Pure Edge forms, which were previously extracted using the process outlined above. Attaching any other type of file may result in the inability to submit your application to Grants.gov.

1) Please attach Attachment 1
2) Please attach Attachment 2
3) Please attach Attachment 3
4) Please attach Attachment 4

ADDITIONAL SENIOR/KEY PERSON PROFILE(S)

Filename

MimeType

Additional Biographical Sketch(es) (Senior/Key Person)

Filename

MimeType

Additional Current and Pending Support(s)

Filename

MimeType

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jeffrey D. Klausner, MD, MPH	POSITION TITLE Professor of Medicine Professor of Public Health
eRA COMMONS USER NAME jklausner	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing,*

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

A. Personal Statement

Jeffrey D. Klausner, MD, MPH, is an internationally recognized expert in the prevention, control and epidemiology of sexually transmitted diseases (STDs) domestically and globally. From 2009-2011 Dr. Klausner was Chief of the CDC PEPFAR HIV and TB program, South Africa. 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, as well as describing the population-based provincial rates of MTCT as part of the South African national PMTCT effectiveness evaluation. Immediately prior, he was the Director of STD Prevention and Control for San Francisco.

Following his work with the CDC in South Africa, Dr. Klausner joined the Department of Medicine at UCLA in the Division of Infectious Diseases and Global Health Program as a Senior Faculty Member and Professor of Medicine and has an appointment in the Department of Epidemiology, School of Public Health as Professor of Public Health. This current proposal builds directly on his interest in global health and more than 15 years of prior STI screening and treatment studies in San Francisco, South Africa and Peru.

Dr. Klausner is the Founding and Senior Editor of the McGraw-Hill Lange text book *Current Diagnosis and Management of Sexually Transmitted Diseases*. In addition, he is a member of the WHO STI Guidelines Committee and frequent advisor to ministries of health on HIV and STI prevention. For this proposal, he will serve as a Co-Principal Investigator and will provide oversight of the research design, implementation and analysis. Given his advisory positions with WHO, the results of this project have the potential to have substantial impact on global health policy to improve birth outcomes in low and middle income countries.

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	Deputy Health Officer/ Director, San Francisco, Department of Public Health, STD Services
1999-2009	Chair, NIMH HIV/STD Intervention Trial, Biological Outcomes Work Group

2004-2011	Associate Clinical Professor of Medicine, University of California, San Francisco
2009-2011	Member, WHO workgroup HIV and STD prevention for MSM and Transgender persons
2009-2011	Chief, HIV and TB Branch, Centers for Disease Control and Prevention, South Africa
2009-2011	Co-Chair, Interagency Workgroup HIV and TB Care and Treatment, South Africa
2012-Present	Professor of Medicine, Geffen School of Medicine, University of California, Los Angeles
2013-Present	Professor of Public Health, Fielding School of Public Health, UC Los Angeles

2002	San Francisco Suicide Prevention Community Award
2002	UCSF Kaiser Award for Excellence in Teaching, nominee
2002	American STD Association, Young Investigator Award
2006	UCSF Association of Clinical Faculty Special Recognition Award
2008	UCSF AIDS Research Institute Sarlo Mentor Award, nominee
2009	Beyond AIDS Nettie Award
2009	CDC Charles C. Shepard Science Award Prevention and Control Category, nominee
2009	UCSF AIDS Research Institute Sarlo Mento Award, nominee
2010	Bay Area's Top Doctors and Dentists Award, Internal Medicine
2010	*Clinical Infectious Diseases* Award for Outstanding Review

C. Selected Peer-Reviewed Publications (of > 340 total)

Most relevant to this application:

Chehab JC, Vilakazi-Nhlapo AK, Vranken P, Peters A, **Klausner JD.** Current integration of tuberculosis (TB) and HIV services in South Africa, 2011. PloS One. 2013;8(3):e57791. doi: 10.1371/journal.pone.0057791. Epub 2013 Mar 4. PMID: 23469242; PMCID: PMC3587619

Cabeza J, García P, Segura E, García P, Escudero F, La Rose S, León S, **Klausner JD.** Feasibility of *Chlamydia trachomatis* screening and treatment in low-risk pregnant women in Lima, Peru: a prospective study in two large urban hospitals. Sex Transm Infect. 2015 Feb; 91(1):7-10. PMID: 25107711

Levy V, Blackmore CS, **Klausner JD**. Self-Collection of Specimens for Nucleic Acid-Based Diagnosis of Pharyngeal, Cervicovaginal, Urethral, and Rectal Neisseria gonorrhoeae and *Chlamydia trachomatis* Infections. *Methods Mol Biol.* 2012;903:407-18. PMID: 22782835.

Renault CA, Israelski DM, Levy V, Fujikawa BK, Kellogg TA, **Klausner JD**. Time to clearance of *Chlamydia trachomatis* ribosomal RNA in women treated for chlamydial infection. Sex Health. 2011 Mar;8(1):69-73. doi: 10.1071/SH10030. PMID: 21371385.

León SR, Konda KA, **Klausner JD**, Jones FR, Cáceres CF, Coates TJ; NIMH Collaborative HIV/STD Prevention Trial Group. *Chlamydia trachomatis* infection and associated risk factors in a low-income marginalized urban population in coastal Peru. Rev Panam Salud Publica. 2009 Jul;26(1):39-45. PMID: 19814880; PMCID: PMC2849276.

Other relevant publications:

Wynn A, Cabeza J, Adachi K, Needleman J, Garcia PJ, **Klausner JD**. Frequency of maternal and newborn birth outcomes, Lima, Peru, 2013. PLoS One. 2015;10(3):e0116102. Epub 2015/03/26. PMID: 25806522; PMCID: PMC4373801

Marlin RW, Young SD, Bristow CC, Wilson G, Rodriguez J, Ortiz J, Mathew R, **Klausner JD**. Piloting an HIV self-test kit voucher program to raise serostatus awareness of high-risk African Americans, Los Angeles. BMC Public Health. 2014 Nov 26;14:1226. PMID: 25427749; PMCID: PMC4289344

Young SD, Daniels J, Chiu CJ, Bolan RK, Flynn RP, Kwok J, **Klausner JD**. Acceptability of using electronic vending machines to deliver oral rapid HIV self-testing kits: a qualitative study. PLoS One. 2014 Jul 30;9(7):e103790. doi: 10.1371/journal.pone.0103790. PMID: 25076208; PMCID: PMC4116256.

Kabanda T, Siedner MJ, **Klausner JD,** Muzoora C, Boulware DR. Point-of-care diagnosis and prognostication of cryptococcal meningitis with the cryptococcal antigen lateral flow assay on cerebrospinal fluid. Clin Infect Dis. 2014 Jan;58(1):113-6. Epub 2013 Sep 24. PMID: 24065327; PMCID: PMC3864499.

Bristow CC, Desgrottes T, Cutler L, Cutler D, Devarajan K, Ocheretina O, Pape JW, **Klausner JD**. The etiology of vaginal symptoms in rural Haiti. Int J STD AIDS. 2013 Dec 18;25(9):669-675. PMID: 24352116.

Guy R, Hocking J, Low N, Ali H, Bauer HM, Walker J, **Klausner JD**, Donovan B, Kaldor JM. Interventions to increase rescreening for repeat chlamydial infection. Sex Transm Dis. 2012 Feb;39(2):136-46. doi: 10.1097/OLQ.0b013e31823ed4ec. Review. PMID: 22249303.

Detels R, Green AM, **Klausner JD**, Katzenstein D, Gaydos C, Handsfield H, Pequegnat W, Mayer K, Hartwell TD, Quinn TC. The incidence and correlates of symptomatic and asymptomatic *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in selected populations in five countries. Sex Transm Dis. 2011 Jun;38(6):503-9. PMID: 22256336; PMCID: PMC3408314.

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;14(6):703-8. Epub 2009/04/28. doi: 10.1111/j.1365-3156.2009.02274.x. PMID: 19392745; PMCID: PMC3625926.

Madhivanan P, Bartman MT, Pasutti L, Krupp K, Arun A, Reingold AL, **Klausner JD**. Prevalence of Trichomonas vaginalis infection among young reproductive age women in India: implications for treatment and prevention. Sex Health. 2009;6(4):339-44. doi: 10.1071/sh09038. PMID: 19917204; PMCID: PMC3619426.

Moss NJ, Ahrens K, Kent CK, **Klausner JD**. The decline in clinical sequelae of genital *Chlamydia trachomatis* infection supports current control strategies. J Infect Dis. 2006 May 1;193(9):1336-8; author reply 1338-9. PMID: 16586376.

D. Research Support

Ongoing Research Support

NIH-NIAID-SBSS-DMID-NIHAI201112 PI: Klausner 07/2013-06/2020
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

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, data quality and interpretation of findings.
Goal: Increase research capacity in Lima, Peru, through studying syphilis in high-risk men

NIH/NIAID. 1R01AI097045 PI: Zetola 09/2011-08/2016
Title: Molecular epidemiology of TB in low and high HIV prevalence settings, Botswana.
Role: Consultant responsible for assisting in intervention development, study design, outcome assessment, and interpretation of findings.
Goal: Understand the transmission of TB in different epidemiologic settings

NIH/NIAID-1R21AI109005-01A PI: Klausner 08/2014-07/2016
Title: Controlling Drug Resistant Gonorrhea with Real-Time PCR Susceptibility Testing
Role: Principal Investigator responsible for overall study implementation
Goal: Develop and evaluate the impact of a new molecular assay for gonorrhea resistance on treatment

NIH-NIMH-1R21HD076685-01A1 PI: DeVieux 07/2013-06/2015
Title: An innovative video/ SMS intervention for newborn medical male circumcision
Role: Co-investigator helping with study design, measurement and evaluation
Goal: Evaluate a brief video on demand for newborn circumcision

CDC-200-2013-N15562 PI: Montoya 09/2013-09/2015
A Waiting Room-Delivered Video to Enhance Antiretroviral Therapy Readiness, Adherence, and Retention in Care 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

Recently Completed Research Support

NIH/NIAID AI28697 UCLA CFAR sub-award PI: Klausner 11/2012-11/2014
Title: Parental decision-making for HIV prevention, Haiti
Role: Principal Investigator responsible for ensuring study implementation and completion
Goal: Identify facilitators for newborn health intervention acceptance

NIH/NIAID CFAR 5P30 AI028697 PI: Coates 09/2013-08/2014
Title: African-American HIV Treatment College
Role: Co-Director responsible for implantation and evaluation
Goal: Increase skills and knowledge of African-American community leaders

NIH/NIDA 3R01DA030234-Suppl PI: Fisher 08/2013-07/2014
Title: Behavioral Science Aspects of rapid test acceptance
Role: Co-investigator responsible for study design, implementation and analysis
Goal: Determine the performance of rapid dual HIV and syphilis tests

NIH/NIMH 5P30MH058107 PI: Rotherham 08/2013-7/2014
Title: CFAR supplement using technology to address HIV/AIDS
Role: Co-investigator responsible for intervention development and study design
Goal: Develop new interventions to increase HIV testing among high-risk men in Los Angeles

NIH-Fogarty Center-D71 PI: Caceres 07/2013-06/2014
Title: Planning a Strategic HIV Population Science Training Program at UPCH in Peru
Role: Co-investigator responsible for proposal development
Goal: Develop and submit a proposal for an HIV science training center

NIH/NIAID AI28697 UCLA CFAR sub-award PI: Klausner 11/2012-11/2013
Title: Parental decision-making for HIV prevention, Haiti
Role: Principal Investigator responsible for ensuring study implementation and completion

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Andrew G.A. Medina-Marino, Ph.D.	Head, Research Unit, Foundation for Professional Development Extraordinary Lecturer, University of Pretoria
eRA COMMONS USER NAME (credential, e.g., agency login) AMEDINA-MARINO	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Swarthmore College	BA	06/2000	Biology/Race Relations
California Institute of Technology	MS	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

Andrew G.A. Medina-Marino, Ph.D., is a molecular biologist and epidemiologist. Currently, Dr. Medina-Marino is head of FPD's Research Unit and acts as Senior Technical Advisor for Disease Surveillance and Laboratory Systems Strengthening. In this capacity, he has developed a portfolio of research activities focused on 1) conducting epidemiological studies on communicable and non-communicable diseases, 2) improving district level capacity to detect and respond to disease outbreaks, 3) increasing district level capacity to use surveillance and epidemiological data for decision making, 4) enhancing pre- and post-analytical laboratory service systems at the point of clinic-lab interface, and 5) developing and evaluating interventions in support of comprehensive health systems strengthening.

Previously, Dr. Medina-Marino was Laboratory Branch Chief for CDC-South Africa, where he was responsible for the management and oversight of ~$16.5M in PEPFAR (*President's Emergency Plan for AIDS* Relief) funds focused on strengthening public health laboratory systems and disease surveillance programs for HIV/AIDS, TB and opportunistic infections. In this capacity, he supported and advised the National Health Laboratory Service (NHLS), South Africa's national pathology service provider, on the expansion of laboratory based surveillance programs. He also worked directly with NHLS and the National Department of Health to develop national point-of-care policy and guidelines. As a Molecular Biologist, Dr. Medina-Marino has conducted research into the molecular mechanisms of NG adherence and invasion and immunological tolerance. Dr. Medina-Marino has worked extensively with the Tshwane District Department of Health and the staff at the two clinics that will serve as enrollment sites.

For this proposal, Dr. Medina-Marino will serve as principal investigator along with Dr. Klausner and will be responsible for the coordination of all in-country study implementation efforts and quality assurance. He will provide direct oversight for the South African-based study team, including study nurses who will have direct contact with patient-participants and data managers.

B. Positions and Honors

Positions and Employment

1995 – 1996 Research Fellow, Rockefeller University
1999 – 2000 Research Fellow, Laboratory of Molecular Systematics, Smithsonian Institution
1997 – 2001 Founder/Editor-in-Chief, The Journal of Young Investigators
2000 – 2001 Research Fellow, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health
2002 – 2008 Howard Hughes Medical Institute Pre-doctoral 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
2001 – Present	Board of Trustees, The Journal of Young Investigators
2011 – 2012	Epidemiologist/Chief, Laboratory Branch, U.S. Centers for Disease Control, South Africa
2012 – Present	Senior Technical Advisor, Disease Surveillance and Laboratory Systems Strengthening, Foundation for Professional Development
2012 – Present	Head, Research Unit, Foundation for Professional Development
2014 & 2015	Epidemiologist, *Médecins Sans Frontières*, West Africa Ebola Response
2014 – Present	Extraordinary Lecturer, School of Health Systems and Public Health, University of Pretoria, South Africa

Awards and Honors

1996	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 Pre-doctoral Fellowship
2010	Donald C. Mackel Award, Centers for Disease Control and Prevention
2011	Remsen Bird Lecture, Occidental College

C. Selected Peer-reviewed Publications

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
5. Lo YC, Dooyema CA, Neri A, Durant J, Jefferies T, **Medina-Marino A**, de Ravello L, Thoroughman D, Davis L, Dankoli RS, Samson MY, Ibrahim LM, Okechukwu O, Umar-Tsafe NT, Dama AH, Brown MJ. Childhood lead poisoning associated with gold ore processing: a village-level investigation-Zamfara State, Nigeria, October-November 2010. Environ Health Perspect. 2012;120(10):1450-5. Epub 2012/07/07. doi: 10.1289/ehp.1104793. PMID: 22766030; PMCID: PMC3491928.
6. **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.

7. Carlisle HJ, Luong TN, **Medina-Marino A***, Schenker L, Khorosheva E, Indersmitten T, Gunapala KM, Steele AD, O'Dell TJ, Patterson PH, Kennedy MB. Deletion of densin-180 results in abnormal behaviors associated with mental illness and reduces mGluR5 and DISC1 in the postsynaptic density fraction. J Neurosci. 2011;31(45):16194-207. doi: 10.1523/jneurosci.5877-10.2011. PMID: 22072671; PMCID: PMC3235477. *(*Note: This was a tri-first authored paper.)*
8. 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.
9. 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.

D. Research Support

Ongoing Research Support

AID-674-A-12-00037 PI: Wolvaardt 10/31/12 – 09/30/17
Title: Factors affecting presentation for first antenatal care visit in Tlokwe sub-district, Northwest Province and Capricorn District, Limpopo Province, South Africa
Role: Sub-Project Primary Investigator
Goals: 1) To describe the sociodemographic and obstetric characteristics of women presenting first ANC visit
2) To determine the proportion of women who presented for first ANC visit after 20 weeks gestation
3) To identify risk factors for presentation for first ANC visit after 20 weeks gestation
4) To compare the socio-demographic and clinical characteristics of those who presented for first ANC visit before 20 weeks gestation and those who presented after 20 weeks gestation.

AID-674-A-12-00017 PI: Wolvaardt 10/31/12 – 09/30/17
Title: 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
Role: Sub-Project Co-Primary Investigator
Goals: 1) To assess the acceptability of the self-collected tampon method,
2) To compare the prevalence of hrHPV mRNA-positivity between clinician- and tampon-collected specimens
3) To assess the accuracy and agreement of self-collected tampons compared to clinician-collected specimens for hrHPV mRNA testing

AID-674-A-12-00017 PI: Wolvaardt 10/31/12 – 09/30/17
Title: In-clinic laboratory services assessment in PHCs and CHCs in Tshwane, Nkangela, Vhembe and Capricorn Districts
Role: Sub-Project Primary Investigator
Goals: 1) Assess and identify gaps in facility level laboratory services
2) Ensure optimal facility-level laboratory testing practices, efficiency in processing specimens and managing test result
3) Develop baseline indicator data in which to compare improvement following interventions

AID-674-A-12-00037 PI: Wolvaardt 10/31/12 – 09/30/17
Title: Identifying barriers to notifiable disease reporting in support of a national HIV drug resistance surveillance system
Role: Sub-Project Primary Investigator
Goals: 1) To determine PHC-level procedural and structural impediments to proper disease notification
2) To improve the identification and reporting of notifiable diseases to District-level authorities
3) To inform the development of PHC-level HIV drug resistance surveillance

AID-674-A-12-00017 PI: Wolvaardt 10/31/12 – 09/30/17

Title: Human Resources, Health and Productivity: Assessing the Impact of Personal Health on Absenteeism, Presenteeism and Attrition in Nurses and Doctors in South Africa

Role: Sub-Project Primary Investigator

Goals: 1) To estimate the frequency of non-communicable diseases, HIV, TB, mental health conditions, interpersonal violence and associated risk factors in South African doctors, nurses and health care managers.
2) To determine the frequency of occupational/work environment exposures that may lead to poor health outcomes
3) To explore associations between putative risk factors and health outcomes
4) To assess the impact of health conditions, risk factors, and occupational work environment exposures on productivity, absenteeism, presenteeism, burn-out and attrition
5) To test the feasibility and acceptability of long-term follow-up of South African study participants
6) To validate the utility of body silhouette images to approximate body mass index (BMI)

Recently Completed Research Support

None

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Ebonwu, Joy Ikechi	Epidemiologist
eRA COMMONS USER NAME (credential, e.g., agency login)	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
School of Medical Laboratory Sciences, University of Benin Teaching Hospital, Nigeria	HND	06/1992	Medical Laboratory Sciences
Tshwane University of Technology, South Africa	BTech	06/2006	Biomedical Sciences
University of Witwatersrand, South Africa	MSc(Med)	06/2010	Medical Microbiology
University of Pretoria, South Africa	MPH	06/2012	Public Health

A. Personal Statement

Joy Ikechi Ebonwu, MPH, is a STI Epidemiologist with FPD. Prior to working for FPD Ms. Ebonwu was an epidemiologist with the Centre for HIV and STIs at the National Institute for Communicable Diseases within the National Health Laboratory Service in South Africa. In that role she worked closely with the South African National Department of Health to support the strategic objectives of the National STI Surveillance Programme.

Ms. Ebonwu is currently assisting in the development and implementation of the first national sentinel STI etiological surveillance project. She has also worked as a laboratory supervisor at National Health Laboratory Service Mycobacteriology referral laboratory in Braamfontein, Johannesburg and has spent considerable time performing diagnostic procedures at the Sexually Transmitted Infections Research Laboratory at George Mukhari Hospital in Pretoria, South Africa. Ms. Ebonwu is a graduate of the South African Field Epidemiology and Laboratory Training Program (a.k.a., The South African EIS) and has a Master of Public Health from the University of Pretoria and a Master of Medical Microbiology from the University of Witwatersrand in Johannesburg.

For this project, Ms. Ebonwu will provide coordination and oversight of all specimen collection, transport, and laboratory processing of all study specimens at the proposed study sites.

B. Positions and Honors

Positions and Employment

1993 – 1994	Intern Technologist, University of Maiduguri Teaching Hospital, Nigeria
1994 – 2002	Medical Laboratory Technologist, Frank Clinic, Lagos, Nigeria
2003 – 2004	Microbiology Intern, George Mukari Hospital, Pretoria, South Africa
	Microbiologist, Sexually Transmitted Infections Research Laboratory, Medical University of Southern Africa
2004 – 2010	Laboratory Supervisor, Mycobacterial Referral Laboratory, National Health Laboratory Services, Braamfontein, Johannesburg

2011 – 2012	FELTP Resident, Field Epidemiology and Laboratory Training Programme, National Institute for Communicable Diseases, Johannesburg
2013 – June 2014	Epidemiologist, Centre for HIV and STIs, National Institute for Communicable Diseases, Johannesburg
July 2014 – present	Epidemiologist, Research unit, Foundation for Professional Development (FPD)

Honors

2007	Gold Award for contributions to Clinical Microbiology in South Africa, BACTLAB SYSTEMS
2013	Merit Certificate, Faculty of Health Science, University of Pretoria

C. Selected Peer-reviewed Publications

1. **Ebonwu JI**, Tint KS, Ihekweazu C. Low treatment initiation rates among multidrug-resistant tuberculosis patients in Gauteng, South Africa, 2011. Int J Tuberc Lung Dis. 2013;17(8):1043-8. Epub 2013/07/06. doi: 10.5588/ijtld.13.0071. PMID: 23827028.
2. **Ebonwu J**, Coetzee G, Koornhof H, Tint K-S, Kuonza L. Newly Diagnosed Multi-Drug Resistant Tuberculosis in Gautent, South Africa, 2004 to 2010. Communicable Diseases Surveillance Bulletin. 2012;10(1):10-3. No PMID.
3. Patel M, **Ebonwu J**, Cutler E. Comparison of chlorine dioxide and dichloroisocyanurate disinfectants for use in the dental setting. SADJ. 2012;67(7):364, 6-9. Epub 2013/08/21. PMID: 23951794.

D. Research Support

None.

BIOGRAPHICAL SKETCH

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

NAME	POSITION TITLE
Wang, Xiaoyan	Adjunct Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) WANGXY2	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Fudan University, China	BS	07/01	Applied Mathematics
University of North Carolina at Chapel Hill	PhD	06/10	Biostatistics

A. Personal Statement

I am an assistant professor in the Department of Medicine Statistics Core at UCLA. I have experience collaborating with researchers in basic science, translational research and clinical trials. My research focuses on the general area of survival analysis, the design and analysis of biomarker studies, which usually involve high-throughput array-based and sequencing technology for transcriptomic, microRNA, proteomic and epigenomic data. Before my current position I served as a senior statistician in the Department of Biostatistics and Biostatistics Shared Resource (BASE Unit) for UCLA's Jonsson Comprehensive Cancer Center for two years. For this project I will oversee all the statistical analyses.

B. Positions and Honors

Positions and Employment

2002 – 2003	Research Assistant, Department of Biostatistics, University of North Carolina at Chapel Hill
2003 – 2004	Research Assistant, School of Nursing, University of North Carolina at Chapel Hill
2004 – 2007	Research Assistant, Center for AIDS Research, University of North Carolina at Chapel Hill
2006	Statistician, Sanofi-Aventis Pharmaceuticals
2007– 2010	Research Assistant, Center for Environmental Medicine, Asthma and Lung Biology, University of North Carolina at Chapel Hill
2010 – 2012	Senior Statistician, Department of Biostatistics, UCLA
2012 – Present	Adjunct Assistant Professor, Department of Medicine, Statistics Core, David Geffen School of Medicine, UCLA

Other Experience and Professional Membership

2007 – present	Member, American Statistical Association
2007 – present	Member, International Biometric Society

C. Selected Peer-reviewed Publications

1. Robert L, Harview C, Emerson R, Wang X, Mok S, Homet B, Comin-Anduix B, Koya RC, Robins H, Tumeh PC, Ribas A. Distinct immunological mechanisms of CTLA-4 and PD-1 blockade revealed by analyzing TCR usage in blood lymphocytes. Oncoimmunology. 2014 Jun 25;3:e29244. eCollection 2014. [PMID: 25083336]

2. Gschweng EH, McCracken MN, Kaufman ML, Ho M, Hollis RP, Wang X, Saini N, Koya RC, Chodon T, Ribas A, Witte ON, Hohn DB. HSV-sr39TK positron emission tomography and suicide

gene elimination of human hematopoietic stem cells and their progeny in humanized mice. Cancer Res 2014 Sep15;74(18):5173-83. doi:10.1158/0008-5472.CAN-14-0376. Epub 2014 Jul 18. [PMID: 25038231].

3. Carbonaro Sarracino D, Tarantal AF, Lee CC, Martinez M, Jin X, Wang X, Hardee CL, Geiger S, Kahl CA, Kohn DB. Effects of vector backbone and pseudotype on lentiviral vector-mediated gene transfer: studies in infant ADA-deficient mice and rhesus monkeys. Mol Ther. 2014 Oct 22(10):1803-16. doi: 10.1038/mt.2014.88. Epub 2014 Jun 13. [PMID: 24925206].
4. Everson RG, Jin RM, Wang X, Safaee M, Scharnweber R, Lisiero DN, Soto H, Liau LM, Prins RM. Cytokine responsiveness of CD8(+) T cells is a reproducible biomarker for the clinical efficacy of dendritic cell vaccination in glioblastoma patients. J Immunother Cancer. 2014 May 13;2:10. doi: 10.1186/2051-1426-2-10. eCollection 2014. [PMID: 24883189].
5. Chodon T, Comin-Anduix B, Chmielowski B, Koya RC, Wu Z, Auerbach M, Ng C, Avramis E, Seja E, Villanueva A, McCannel TA, Ishiyama A, Czernin J, Radu CG, Wang X, Gjertson DW, Cochran AJ, Cornetta K, Wong DJ, Kaplan-Lefko P, Hamid O, Samlowski W, Cohen PA, Daniels GA, Mukherji B, Yang L, Zack JA, Kohn DB, Heath JR, Glaspy JA, Witte ON, Baltimore D, Economou JS, Ribas A. Adoptive transfer of MART-1 T-cell receptor transgenic lymphocytes and dendritic cell vaccination in patients with metastatic melanoma. Clin Cancer Res. 2014 May 1;20(9):2457-65. doi: 10.1158/1078-0432.CCR-13-3017. Epub 2014 Mar 14. [PMID: 24634374].
6. Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, Mok S, Huang RR, Cochran AJ, Comin-Anduix B, Koya RC, Graeber TG, Robins H, Ribas A. CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res. 2014 May 1:20(9):2424-32. doi:10.1158/1078-0432.CCR-13-2648. Epub 2014 Feb 28. [PMID: 24583799].
7. Carbonaro DA, Zhang L, Jin X, Montiel-Equihua C, Geiger S, Carmo M, Cooper A, Fairbanks L, Kaufman ML, Sebire NJ, Hollis RP, Blundell MP, Senadheera S, Fu PY, Sahaghian A, Chan RY, Wang X, Cornetta K, Thrasher AJ, Kohn DB, Gaspar HB. Preclinical demonstration of lentiviral vector-mediated correction of immunological and metabolic abnormalities in models of adenosine deaminase deficiency. Mol Ther. 2014 Mar;22(3):607-22. doi: 10.1038/mt2013.265. Epub 2013 Nov 20. [PMID: 24256635]
8. Krysan K, Cui X, Gardner BK, Reckamp KL, Wang X, Hong L, Walser TC, Rodriguez NL, Pagano PC, Garon EB, Brothers JF 2nd, Elashoff D, Lee JM, Spira AE, Sharma S, Fishbein MC, Dubinett SM. Elevated neutrophil gelatinase-associated lipocalin contributes to erlotinib resistance in non-small cell lung cancer. Am J Transl Res. 2013 Aug 15;5(5):481-96. eCollection 2013. [PMID 23977408]
9. Romero Z, Urbinati F, Geiger S, Cooper AR, Wherley J, Kaufman ML, Hollis RP, de Assin RR, Senadheera S, Sahagian A, Jin X, Gellis A, Wang X, Gjertson D, Deoliveira S, Kempert P, Shupien S, Abdel-Azim H, Walters MC, Meiselman HJ, Wenby RB, Gruber T, Marder V, Coates TD, Kohn DB.
β-globin gene transfer to human bone marrow for sickle cell disease. J Clin Invest. 2013 Jul 1. pii:67930. doi: 10.1172/JCI67930. [PMID 23863630].
10. Birkhäuser FD, Rampersaud EN, Wang X, Kroger N, Zomorodian N, Riss J, Li G, Kabbinavar FF, Pantuck AJ, Belldegrun, AS. Salvage Targeted Kidney Cancer Therapy in Patients Progressing on High Dose Interleukin-2 Immunotherapy: The UCLA Experience. Cancer J. 2013 May-Jun;19(3):189-96. doi: 10.1097/PPO.0b013e318292e8a4 [PMID: 23708063]
11. Geiser M, Lay JC, Bennett WD, Zhou H, Wang X, Peden DB, Alexis NE. Effects of ex vivo gamma-tocopherol on airway macrophage function in healthy and mild allergic asthmatics. J Innate Immun. 2013;5(6):613-24. doi: 10.1159/000350234. Epub 2013 May 8 [PMID: 23689260; PMCID: PMC3939603]
12. Matse HJ, Yoshizawa J, Wang X, Elashoff D, Bolsher JG, Veerman EC, Bloemena, E., and Wong, DT. Discovery and pre-validation of salivary extracellular microRNA biomarkers panel for the non-

invasive detection of benign and malignant parotid gland tumors. Clin Cancer Res. 2013 Jun 1;19(11):3032-8. doi: 10.1158/1078-0432.CCR-12-3505. Epub 2013 Apr 10. [PMID: 23575476]

13. Corselli M, Parekh C, Sahaghian A, Wang W, Ge S, Chin CJ, Wang X, Montelatici E, Lazzari L, Crooks, GM, and Peault B. Perivascular support of human hematopoietic stem/progenitor cells. Blood, 2013 Apr 11;121(15): 2891-901. doi: 10.1182/blood-2012-08-451864. Epub 2013 Feb 14 [PMID: 23412095; PMCID: PMC3707421]
14. Candotti F, Shaw KL, Muul L, Carbonaro D, Sokolic R, Choi C, Schurman SH, Garabedian E, Kesserwan C, Jagadeesh GJ, Fu PY, Gschweng E, Cooper A,Tisdale JF, Weinberg KI, Crooks GM, Kapoor N, Shah A, Abdel-Azim H, Yu XJ, Smogorzewska M, Wayne AS, Rosenblatt HM, Davis CM, Hanson C, Rishi RG, Wang X, Gjertson D, Yang OO, Balamurugan A, Bauer G, Ireland JA, Engel BC, Podsakoff GM, Hershfield MS, Blaese RM, Parkman R, Kohn DB. Gene therapy for adenosine deaminase-deficient severe combined immune deficiency: clinical comparison of retroviral vectors and treatment plans. Blood. 2012 1;120(18):3635-46. doi: 10.1182/blood-2012-02-400937. Epub 2012 Sep 11. doi:10.1182/blood-2012-02-400937 [PMID: 22968453; PMCID: PMC3488882]
15. Carbonaro, D., Jin, X., Wang, X., Yu, XJ, Rozengurt, N., Kaufman, ML, Blackburn, MR, Kohn, DB, et al. Gene Therapy and Bone Marrow Transplant in ADA-deficient Mice: Roles of Enzyme Replacement Therapy and Cytoreduction. Blood. 2012 doi:10.1182/blood-2012-02-408591. [PMID: 22833548; PMCID: PMC3488883].

D. Research Support

Ongoing Research Support

Disease Team II: DR2A-05309 Ribas (PI) 01/01/13-12/29/18
CIRM grant: Genetic Re-programming of Stem Cells to Fight Cancer
Role: Co-Investigator
Goal: To develop an Investigational New Drug (IND) and fully enroll a phase I clinical trial within the grant period to genetically redirect the patient's immune response to specifically attack the cancer starting from hematopoietic (blood) stem cells (HSC) in patients with advanced forms of the aggressive skin cancer malignant melanoma.

1U01AI100801-01 Kohn (PI) 08/01/12-07/31/17
EFS-ADA LENTIVIRAL VECTOR TRANSDUCTION OF BONE MARROW CD34+ CELLS FOR ADA-SCID
Role: Co-Investigator
Goal: To seek to develop better treatments for Primary Immune Deficiency (PID) disorders, using lentiviral vectors to transfer the normal gene to bone marrow stem cells. It will provide first-in-human information on the safety and effectiveness of this combined cell and gene therapy approach and would support the development of better treatments for PID and other blood cell diseases.

Disease Team: DR1-01452 Kohn (PI) 01/01/11-12/29/16
CIRM grant: Stem Cell Gene Therapy for Sickle Cell Disease
Role: Co-Investigator
Goal: To develop a clinical trial to evaluate a novel treatment for patients with sickle cell disease, using their own adult blood-forming stem cells, after correcting the hemoglobin gene defect. Successful treatment of sickle cell disease using adult blood forming "hematopoietic" stem cells corrected with gene therapy may provide a clinically beneficial way to treat sickle cell disease with greater safety and wider availability than current options.

NIH/NIAID-1R21AI109005-01A Klausner (PI) 08/15/2014-07/31/16

Controlling Drug Resistant Gonorrhea with Real-Time PCR Susceptibility Testing
Role: Principal Investigator responsible for overall study implementation
Goal: Develop and evaluate the impact of a new molecular assay for gonorrhea resistance on treatment

1UL1RR033176-01 Dubinett (PI) 06/01/11-02/29/16
UCLA Clinical and Translational Science Institute
Role: Co-Investigator: Biostatistics, Study Design and Clinical Data Management Program
Goal: The CTSI will create the infrastructure for clinical and translational research among a 4-instution consortium that includes UCLA, UCLA-Harbor Biomed, Cedars Sinai Medical Center, and Charles Drew University.

Completed Research Support

NIH 1P01CA132681-01A2 Baltimore (PI) 05/03/10-07/01/12
NCI/Stem Cell-Engineered Tumor Immunity in Man
Role: Statistician
Goal: To lay the basic and translational science foundation for the engineering of the immune system through genetic modification of T cells, hematopoietic stem cells and embryonic stem cells.

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1. Project Director/Principal Investigator (PD/PI)

Prefix: Dr.

*First Name: Jeffrey

Middle Name:

*Last Name: Klausner

Suffix: MD

2. Human Subjects

Clinical Trial? [X] No [ ] Yes

*Agency-Defined Phase III Clinical Trial? [ ] No [ ] Yes

3. *Disclosure Permission Statement

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

[X] Yes [ ] No

4. *Program Income

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

[ ] Yes [X] 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)

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

*Does the proposed project involve human embryonic stem cells? [X] No [ ] Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): [ ] Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

*Inventions and Patents: [ ] Yes [X] No

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

*Previously reported: [ ] Yes [ ] No

7. Change of Investigator / Change of Institution Questions

[ ] Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

[ ] Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

Please attach applicable sections below.

1.	Introduction to Application (for RESUBMISSION or REVISION only)	Intro_Responses1033653671.pdf	Mime Type: application/pdf
2.	Specific Aims	Specific_Aims1033653989.pdf	Mime Type: application/pdf
3.	*Research Strategy	Research_Narr1033653855.pdf	Mime Type: application/pdf
4.	Progress Report Publication List		

Human Subjects Sections

5.	Protection of Human Subjects	human_subjects1033653856.pdf	Mime Type: application/pdf
6.	Inclusion of Women and Minorities	inclusion_of_women_and_minorities1033653674.pdf	Mime Type: application/pdf
7.	Inclusion of Children	INCLUSION_OF_CHILDREN1033654083.pdf	Mime Type: application/pdf

Other Research Plan Sections

8.	Vertebrate Animals		
9.	Select Agent Research		
10.	Multiple PD/PI Leadership Plan	multi_PI1033653666.pdf	Mime Type: application/pdf
11.	Consortium/Contractual Arrangements	Consortium_Agreement_rev1033653676.pdf	Mime Type: application/pdf
12.	Letters of Support	Letters_of_Support1033654087.pdf	Mime Type: application/pdf
13.	Resource Sharing Plan(s)	resource_sharing_plan1033653677.pdf	Mime Type: application/pdf

Appendix (if applicable)

14. Appendix

Appendix 1	Appendix_1_Pregnancy_Outcomes1033654002.pdf	Mime Type: application/pdf
Appendix 2	Appendix_2_Data_Collection_Tools1033654003.pdf	Mime Type: application/pdf

Introduction to 1 R21 HD084274-01: The reviewers believed this to be "a very strong application focusing on a very important and vulnerable population," that "would have a substantial impact on public health in South Africa and could serve as a model to middle and low income countries" and that "the principal investigator and his collaborators are very well qualified to carry out this study." Our response addresses all identified weaknesses:

Reviewer Comment 1: "their partners should also be screened since they can re-infect the woman"
Response 1: We agree; we have added text to the *Reporting and Treatment* section of C.5, Aim 1, and will now include partner referral and partner treatment packs. Ensuring partner treatment will also be addressed by clinical roving teams, as described in the *Potential Challenges and Quality Assurance* section of C.5, Aim 1.

Reviewer Comment 2: "the study design does not include rescreening at later time-points"
Response 2: We agree; we have added text to the section on *Reporting and Treatment* section of C.5, Aim 1, and will routinely conduct rescreening at week 32 of pregnancy.

Reviewer Comment 3: "no justification…for the differential inclusion criteria for…treatment & control groups"
Response 3: Our aim is to evaluate the feasibility of integrating the STI screening intervention into the basic antenatal care services provided during the first ANC visit. While ideally the comparison group would be recruited and enrolled at a similar first ANC visit, to maximize timely recruitment and enrollment the control group will be recruited at multiple time points during their ANC. As is now explained in the *Analysis* section of C.5, Aim 2, we will analyze by ANC visit number at enrollment to control for impact on birth outcomes.

Reviewer Comment 4: "not clear how Aim 1 addresses acceptability & feasibility of [STI screening/treatment]"
Response 4: To improve clarity, we have revised the language in Specific Aim 1a, and relocated our definitions of acceptability and feasibility to the *Analysis* section of C.5, Aim 1. In that section we also now describe that we will capture data on the numbers of women offered but refusing testing, along with reasons for refusal.

Reviewer Comment 5: "Inclusion of an implementation scientist would have strengthened the team"
Response 5: As former CDC medical officer and local public health officer from 1995-2011, Dr. Klausner has conducted several PEPFAR, State and CDC-funded implementation science projects and is highly experienced in implementation science, continuous quality improvement and translating research into practice. To further strengthen the team we have also added Dr. Margot Uys, a well-respected implementation science expert in PMTCT and service integration working with FPD in South Africa.

Reviewer Comment 6: "More information is needed on the propensity score matching, since this is a more rigorous approach to non-randomized controlled trials, and strengthens the approach. There needs to be description of the matching variables, and how the analysis will be conducted."
Response 6: Detailed information about propensity score matching and analysis has been added to C.6.

Reviewer Comment 7: "study would benefit from qualitative implementation interviews with provider/patients"
Response 7: We agree. As now described in the *Analysis* section of C.5, Aim 1, we will complete qualitative interviews with patients using a recently adapted tool (see Appendix 2.D); providers will provide qualitative input via brief 1:1 interviews twice during the year-long implementation period. Additionally, an anonymous "suggestion box" will be made available to providers who may wish to provide feedback but are not comfortable sharing concerns during regular biweekly in-person team meetings.

Reviewer Comment 8: "It is not clear why the NG and CT POC testing is not being done in real time for symptomatic individuals. This is a significant missed opportunity for treatment of infected individuals"
Response 8: Treatment will be done in real time for those symptomatic. South Africa introduced STI syndromic management into primary healthcare approximately 10 years ago. As is now clarified in the *Recruitment and Eligibility* section of C.5, Aim 1, per that protocol symptomatic individuals are immediately provided treatment that will cover STIs: Azithromycin for CT and Ceftriaxone for NG. Adherence to those treatment guidelines will thus negate the concern for missed opportunities related to lack of real-time testing.

Reviewer Comment 9: "Gestational age assessment would be improved with ultrasound evaluation"
Response 9: Ultrasound is not available in primary health care clinics in South Africa; at first ANC visit, gestation age is calculated from the first day of last menstrual period and/or symphysis-fundal height (SFH). Pregnant women may be referred for gestational age estimation via ultrasound if medically indicated, such as in cases of vaginal bleeding, small fundal height based on date of last period, or absence of fetal movements. Based on current data only about 5% of women attending ANC receive an ultrasound; as is now described in the *Recruitment and Eligibility* section of C.5, Aim 2, we will compare clinically collected ultrasound results for gestational age documented in the ANC medical record with the estimated gestational age to assess the quality of the gestational age estimated at the first ANC visit.

Reviewer Comment 10: "It is not clear…what the coverage rates for Option-B and vertical transmission rates are for the 2 clinics in the study;" "No power calculation [for] HIV infection among live-born infants is provided"
Response 10: Option B coverage and vertical transmission rates have been clarified in section C.2. The power calculation has now been added to section C.6 of the narrative.

SPECIFIC AIMS

Globally, an estimated 235,000 newborns are infected annually with HIV through maternal-to-child intrapartum/peripartum transmission.[1] While "Option B and B+"HIV treatment programs for pregnant women are increasingly scaled up, even in well-performing programs mother-to-child transmission (MTCT) of HIV still occurs.[1] In order to reach the UNAIDS goals of zero new infections and the elimination of MTCT of HIV infection, co-factors that increase MTCT of HIV infection must be addressed.[2]

Recent research by our group from a sub-study of NICHD HPTN 040 demonstrated that the sexually transmitted infections *Neisseria gonorrhoeae* (NG) *and Chlamydia trachomatis*(CT) conferred a 2.6 times increased risk of mother-to-child HIV transmission.[3] In that sub-study of 1373 HIV-positive pregnant women tested for NG and CT, 24.2% of the HIV MTCT was attributable to NG and CT co-infection.[4] Our work confirmed a prior 2001 study in Tanzania demonstrating that among HIV-infected pregnant women co-infection with NG was associated with a 5.5 times increased risk of intrauterine HIV transmission.[5]NG and CT have long been known to increase the sexual transmission of HIV through their effects on genital inflammation, increased genital HIV viral load and increases in target cell activation, but no research has explored the role and potential impact of screening and treatment of NG and CT infections in maternal-to-child HIV transmission in the modern era of treating HIV-infected pregnant women with combination antiretroviral therapy.

The WHO estimates there are 105.7 million and 106.1 million new cases annually of CT and NG infection, respectively, making these infections the most common bacterial sexually transmitted infections globally.[6] Large studies using current molecular-based diagnostic technology documenting the problem of CT and NG in pregnant women are lacking in Africa, and those existing suggest similar if not higher CT and NG prevalence than those reported by the WHO.[7-11]HIV-infected women have higher rates of CT and NG infection than HIV-uninfected pregnant women.[12] The singular focus on MTCT HIV prevention has resulted in the neglect of CT and NG treatment in pregnant women and missed opportunities to reduce devastating STI-related adverse pregnancy outcomes including the impact of STIs on MTCT of HIV infection.[12-15]

South Africa has an estimated preterm delivery rate of 8 per 100 live-births, resulting in more than 80,000 preterm births annually. Preterm birth is associated with about 60% infant mortality.[16] In addition, with one of the largest number of HIV-infected pregnant women delivering annually in the world (>300,000),[17]both adverse birth outcomes and MTCT HIV are significant public health problems; however, few studies have systematically measured the role of STIs and adverse birth outcomes in HIV-infected South African women.

In response to the need for further research to eliminate MTCT of HIV infection and reduce infant morbidity and mortality, we propose a study to investigate the acceptability and feasibility of CT and NG screening in pregnant women and the potential impact of such a screening program on the MTCT of HIV infection. Two antenatal clinics in Tshwane District, Gauteng Province, South Africa, will provide a unique setting to study those issues in further detail.

Our proposed project has the following two Specific Aims:

Specific Aim 1: To determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit.

1(a): To determine the proportion of eligible women consenting to testing (acceptability) and NG/CT-infected women receiving treatment within two weeks of specimen collection (feasibility)

1(b): To estimate the prevalence of CT and NG in HIV-infected pregnant women attending their first antenatal visit in Tshwane District, South Africa

1(c): To examine correlates of prevalent CT and/or NG infection and CT/NG treatment outcomes among pregnant women in the study

Specific Aim 2: To describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit.

2(a): To estimate the frequency of adverse birth outcomes such as premature rupture of membranes, preterm labor or delivery, and small for gestational age, and their association with CT and NG screening and treatment

2(b): To estimate the frequency of HIV MTCT and its association with CT and NG screening and treatment

As South Africa aims for ZERO new HIV infections from MTCT, identifying and eliminating putative risk factors to MTCT is of utmost importance. The collaboration between the Foundation for Professional Development (FPD) South Africa and the UCLA Program in Global Health will improve local capacity to conduct high-level research and epidemiological studies, ultimately strengthening South Africa's ability to contribute to the global body of biomedical and public health knowledge.

RESEARCH STRATEGY

A.SIGNIFICANCE

HIV and STIs among pregnant women in South Africa are a critical problem. In 2011, the most current year for which data are available, the South African government estimated that 29.5% of women seeking antenatal care (ANC) were HIV-positive,[18] a prevalence that has remained relatively stable since 2007. Such high levels of HIV prevalence are further compounded by the high rates of STIs in women of reproductive age, and more specifically, pregnant women. A recent study in Tshwane District found that 26% of women patients at a termination of pregnancy clinic had single, double or triple infections of CT, NG, or *Trichomonas vaginalis.*[19] Infants in South Africa routinely receive chloramphenicol antibiotic eye ointment at birth to prevent neonatal bacterial conjunctivitis, most often caused by untreated maternal CT or NG.[20] Yet the risks to infants are greater than this; our recent analysis in a sub-study of NICHD HPTN 040[3] highlights the increased risk of HIV MTCT in the presence of dual CT/NG infection (see Table 1). Given that most NG and CT infections are asymptomatic in women and that government health programs in South Africa do not routinely screen asymptomatic pregnant women for such STIs, the true burden of disease from STIs in pregnant women is likely higher than statistics suggest.

Table 1. HIV MTCT and CT/NG, South Africa, Brazil, Argentina & US, HPTN 040

Characteristic	CT/NG co-infection	CT/NG uninfected	RR of MTCT	PAF[4]	P-value
HIV+ pregnant women	25	800			
HIV MTCT	5	62			
% HIV transmission	20.0%	7.8%	2.6 (1.1 – 5.8)	24.2%	<.0001

MTCT may be associated with genital tract HIV shedding, CT, and NG. It has been hypothesized that co-existing bacterial STIs (CT and NG) in pregnancy may impact HIV maternal-to-child transmission.[21] However, to date few studies have investigated their effects on vertical HIV transmission. Prior research in non-pregnant women has suggested that co-infection with STIs in HIV-infected women may augment the risk of HIV transmission by increasing viral shedding,[22-25] and subsequent treatment of these STIs can reduce the risk of HIV transmission.[26,27] Limited existing research has suggested that the presence of STIs in HIV-infected pregnant women may increase the risk of HIV MTCT. One study of HIV-infected women in Tanzania reported that co-infection with NG was associated with a 5.5-fold increased risk of intrauterine HIV transmission.[5]

There continues to be room for improvement with PMTCT and Option B in South Africa. In 2004-2005, it was estimated that AIDS contributed to about 40% of all child deaths under age five in South Africa.[28] In 2008 the South African government launched the national PMTCT Accelerated Plan (Option A). While the number of HIV-exposed infants remained stable (230,000-240,000) between 2008 and 2010, the number of infants with a positive HIV PCR result dropped from 9.6% to 3.5%, respectively, with a MTCT rate ranging across the provinces from 1.4% to 5.9%.[29,30] Though tempered by a low (35.1%) uptake of early infant diagnosis testing, significant progress has been made in nationally enhancing coverage of PMTCT services. However, significant variability remains in PMTCT service coverage and quality nationally. In 2013, the South African National Department of Health updated their PMTCT guidelines, hewing closely to the WHO's Option B recommendations; however, MTCT of HIV still occurs and in some provinces is higher than 5%.[31]

B. INNOVATION

The current proposed study will help fill critical gaps in the understanding of how bacterial STIs may impact MTCT of HIV infection in the era of combination ART in pregnant women. Given the high prevalence of HIV infection among pregnant women in South Africa (over 300,000 HIV-infected women deliver annually[17]) and the high prevalence of STIs in women of reproductive age**,** South Africa provides an ideal setting to understand these multifaceted, overlooked interactions. At present, little is known about the ways in which bacterial STIs in pregnancy may impact MTCT of HIV.

Currently, prenatal screening for bacterial STIs is not routinely conducted in low and middle-income countries around the world. While South African policy stipulates that pregnant women are to be screened for HIV and syphilis during their first ANC visit, routine antenatal screening for asymptomatic infection is not conducted for CT or NG. Studies such as this one may help enhance our understanding of the prevalence, impact and attributable risk of CT and/or NG infections and MTCT of HIV. Furthermore, given the known adverse consequences of CT and NG on maternal-child health outcomes, this study may be able to directly inform public health programs and policy to improve the health and wellness of women and children. Finally, in high risk populations such as pregnant women with HIV, screening for CT and NG may have additional benefits by decreasing the risk of preterm birth, low birth weight, neonatal conjunctivitis, pneumonia and infant death.

This study is novel and innovative in 3 primary ways:

1) This pilot study is designed to determine the acceptability and feasibility of routinizing CT/NG screening and treatment of HIV-infected pregnant women attending ANC visits using the recently FDA-cleared commercially available point-of-care CT/NG molecular assay [Xpert CT/NG, Cepheid, Sunnyvale, CA].

Molecular CT/NG screening is not currently available in most low and middle-income countries globally; however, the Cepheid Xpert CT/NG assay is easy to use and allows for decentralized, non-laboratory-based clinic test. It is ideally positioned for uptake in low and middle income settings. The Cepheid Xpert MTB/RIF testing platform is already widely deployed in southern Africa and used for rapid diagnosis in tuberculosis. The addition and use of another test cartridge (CT/NG) is quite feasible.

2) The study findings will enhance knowledge of the prevalence of maternal CT and NG infections as well as related birth outcomes in high risk populations in South Africa. While preliminary research including work by this study team has demonstrated an association between bacterial STIs and poor birth outcomes,[32] these interactions are not yet widely understood and thus evidence to support efforts to prevent and treat CT and NG in pregnant women in low and middle-income countries is urgently needed.
3) The study findings will enhance knowledge about how CT and NG may influence MTCT of HIV, especially for pregnant women in high prevalence populations. As PMTCT programs continue to increase and improve throughout the world, too often these efforts are narrowly focused. A more comprehensive understanding of the role of co-infection with bacterial STIs and the impact this has on MTCT of HIV will serve to greatly improve the effectiveness of these HIV PMTCT programs.

For the reasons outlined above, this study has the potential to significantly inform programs aimed at the prevention of HIV MTCT in South Africa in the era of Option B policy, and to directly impact clinical and public health practices in low and middle-income countries relating to maternal-child health, especially relating to bacterial STIs in pregnancy. If shown to be acceptable, feasible, and potentially efficacious, the pilot intervention from this study will serve as a basis for larger well-controlled clinical trials in the future.

C. APPROACH

The Foundation for Professional Development (FPD) has a standing Memoranda of Understanding with the Gauteng Provincial Dept. of Health to support clinic-based health systems strengthening in Tshwane District. As such, this study will leverage our already strong relationship with both provincial and district health departments.

C.1. Overview and Timeline. This study encompasses 3 phases, as detailed in Table 2:

- ***Phase I:*** Development and piloting of recruitment, enrollment, data collection tools, study staff training and finalization of screening, laboratory, and treatment protocols
- ***Phase II:*** Recruiting and enrolling 600 intervention participants and 600 participants in a comparison group; intervention will be provided as described in section C.5.
- ***Phase III:*** Data analysis, dissemination of findings, and preparation for future research.

Table 2: Study Timeline

Phase	Start	Finish	Year 1				Year 2			
			Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
I	09/15	02/16	■	■						
II	03/16	02/17			■	■	■	■		
III	03/17	08/17							■	■

C.2. The Study Setting. This study will take place in two antenatal clinics in Tshwane District (Pretoria), Gauteng Province, South Africa: 1) KT Motubatse Clinic, which in 2014 had a monthly head count of 130 first time ANC visits, and an annual maternal HIV positivity rate of 21%, an Option-B coverage of 83.5%, and an infant 1st test HIV-positivity rate of 1.3 - 5.3%; and 2) Soshanguve Community Health Center, which had a 2014 monthly head count of 151 first time ANC visits, and an annual maternal HIV positivity rate of 16.8%, an Option-B coverage of 89.4%, and an infant 1st test HIV positivity rate of 0.2 - 4.2% (District Health Information System, 2014). A letter of support for the Tshwane District Department of Health is included with this proposal.

C.3. The Research Team. Jeffrey Klausner, MD, MPH (UCLA PI): Dr. Klausner is an infectious disease epidemiologist and Professor of Medicine and Public Health at UCLA. From 2009-2011 Dr. Klausner was Branch Chief for HIV and TB at the US Centers for Disease Control and Prevention in South Africa. In that role Dr. Klausner worked directly with national, provincial and district health authorities and local non-governmental organizations including FPD to support the national scale-up of PMTCT services. He played a key role in describing the population-based provincial rates of MTCT as part of the national PMTCT effectiveness evaluation.[29,33-35] He will devote 0.10 FTE, and will oversee research design, implementation, and analysis.

Andrew Medina-Marino, PhD (FPD PI) is Head of FPD's Research Unit and Senior Technical Advisor for Laboratory and Disease Surveillance Systems Strengthening activities. Previously, Dr. Medina-Marino was Laboratory Branch Chief for CDC-South Africa, and worked directly with National Health Laboratory Service (NHLS) and the National Department of Health to develop national point-of-care guidelines. Dr. Medina-Marino has worked extensively with the Tshwane District Dept. of Health and the staff at the two clinics that will serve as study sites. For this project he will provide direct oversight for the South African-based study team, including study nurses who will have direct contact with patient-participants and data managers. He will devote 0.20 FTE and will oversee and ensure quality of all in-country study implementation efforts.

Joy Ikechi Ebonwu, MPH (Co-Investigator): Ms. Ebonwu is a STI Epidemiologist with FPD. Prior to working for FPD Ms. Ebonwu was an epidemiologist with the Centre for HIV and STIs at the National Institute

for Communicable Diseases within the NHLS. For this project, Ms. Ebonwu will provide coordination and oversight of all specimen collection, and laboratory processing of all study specimens at both study sites.

Xiaoyan Wang, PhD (Co-Investigator): Dr. Wang is an Assistant Professor in biostatistics within the Statistics Core of the UCLA Department of Medicine. She has extensive experience with design and analysis of large-scale studies. She will devote 0.05 FTE and be responsible for all statistical analyses for this project.

James McIntyre, MBChB (Consultant): Dr. McIntyre is an OB/GYN physician-scientist and internationally-recognized expert on HIV MTCT. He is the executive director of the Anova Health Institute, and the international vice-chair of the NIH-funded International Material Paediatric and Adolescent AIDS Clinical Trials Network (IMPAACT). He regularly serves as a consultant on these issues to the WHO, UNAIDS, and UNICEF. He will provide approximately 2 hours of consultation each month for both years of this project.

Margot Uys, MBChB (Consultant): Dr. Uys is an expert in implementation science, currently supervising USAID and CDC-funded TB and HIV programs related to MTCT, laboratory and supply chain management, and community-based services in 11 districts throughout urban and rural South Africa. She has almost a dozen peer-reviewed publications related to implementation science in a number of topic areas. She will provide approximately 2 hours of consultation each month for both years of this project.

C.4. Preliminary Studies. NICHD HPTN 040 sub-study. The NICHD HPTN 040 parent trial was a randomized multi-center clinical trial in Brazil, South Africa, Argentina, and the U.S. that enrolled 1684 HIV-exposed infants from HIV-infected mothers without prior antiretroviral use.[36] In our UCLA sub-study (Klausner, PI), we used remnant urine specimens from the pregnant female participants, tested those for CT/NG infection using the testing platform we will use in this proposed study [Xpert CT/NG, Cepheid, Sunnyvale, CA], and described the prevalence of CT and NG infections. Among the 409 HIV-infected pregnant South African participants the prevalence of CT was 21.3% and NG, 7.6%. Women with dual CT and NG infection were twice as likely to vertically transmit HIV than those without either infection.[3]

Pilot Study: Lima, Peru, Nov 2012 – May 2013. Most recently, the UCLA team (Klausner, PI) completed a large NIH-funded acceptability and feasibility study of CT screening among pregnant women(N=600) in ANC at 2 large urban hospitals in Lima, Peru.[37,38] Over a 2 month period, 640 patients were approached and 600 enrolled (approximately 300 patients/month with a 94% enrollment rate and 98% treatment rate). The average age of women participants was 27.3 $\pm$ 6.8 years (range 16-47) with an average of 2.3$\pm$ 2.6 lifetime partners (range 1-50), and an average gestational age of 26.3 $\pm$ 10.6 weeks (range 4-41). CT prevalence in the study population was high at 10% (95% CI 7.7 – 12.7%). Prevalence decreased with age, with women 16-23 years having the highest prevalence (15.6%), and the lowest prevalence in women $\geq$ 31 years (5.2%).

Overall, 59 (98%) of the 60 CT-infected pregnant women were treated (1 refused), and 52/59 (88%) returned for test of cure; 100% of these women were treated successfully. CT screening and treatment in pregnancy was both feasible and highly acceptable in this patient population. All infected women were offered partner treatment and 93% either brought partners to the clinic or brought home additional medicine for partners.

Maternal and infant outcome data were also collected on a retrospective convenience sample of 249 patients of the pilot study (see Appendix 1 for details on outcomes). The median gestational age was 39 weeks; with preterm delivery rates of around 6%. Of note, data were not collected on preterm labor rates; however, premature rupture of membranes was 3.6%. 1.6% of patients had low birth weight, with one stillbirth (0.4%).[39]

C.5. Methodology and Study Aims.

Specific Aim 1: To determine the acceptability and feasibility of screening and treating HIV-infected pregnant women for NG and CT at first antenatal care visit.

Methods and Procedures

In order to accomplish Specific Aim 1we will conduct a cross-sectional study among HIV-infected pregnant women who are receiving ANC at either of our two collaborating clinic sites. Through this we plan to achieve two subaims: 1(a): To estimate the prevalence of CT and NG in HIV-infected pregnant women attending their first antenatal visit in Tshwane District, South Africa, and 1(b): To examine correlates of prevalent CT and/or NG infection and treatment outcomes among pregnant women in the study.

Recruitment and Eligibility: We will recruit 600 study participants from pregnant women presenting for ANC services at the two study clinics in Tshwane District, Pretoria, South Africa. Together those 2 clinics see about 250 new women each month for ANC. Eligible criteria include: 1) Age $\geq$ 18 years, 2) Currently pregnant, 3) Documented HIV infection, 4) Attending the first ANC visit for this pregnancy, 5) Willingness to self-administer a vulvo-vaginal swab, 6) Residence in Tshwane district, and 7) Intent to stay in Tshwane district through delivery.

Clinic staff and study recruiters will be trained in the study methods and human subjects' research. They will also receive training on South Africa's syndromic management algorithms for STIs, which requires immediate treatment for all symptomatic individuals with Azithromycin for CT and Ceftriaxone for NG as part of the

standard of care in South Africa. Patients will be preliminarily screened for eligibility via chart review at the time of the appointment; all those suspected to be eligible will be formally screened during the visit by study nurses. All eligible patients will be provided specific information about CT and NG infection, the consequences and treatment of those infections, study risks and benefits, and invited to participate. Those providing informed consent will be enrolled, instructed on how to self-collect a vaginal swab specimen and asked to share several forms of detailed contact information (e.g., personal, family, friend, residence, and work) to assure follow-up. Those who are eligible but choose *not* to enroll will be asked to provide reasons for refusal, and basic sociodemographic information will be gathered when possible. This information will be an important factor in our measures of acceptability of STI screening at first ANC visit. Women who are currently pregnant with documented HIV infection but otherwise ineligible will be logged with reason for ineligibility; data will be used for descriptive analysis of the differences between our study population and the general ANC patient population.

A data collection instrument (see Appendix 2A) will be used to collect demographic, socio-behavioral characteristics, knowledge related to CT/NG/HIV effect on pregnancy, pregnancy history, and other relevant clinical information. Those data will be abstracted from patient medical records and interviews by study nurses.

Specimen Collection, Transport, Processing and Storage: Eligible participants will be asked to provide a self-collected vulvo-vaginal swab specimen during their visit. Specimens will be handed to a trained nurse who will label them with a unique study barcode and place them in a secure storage area for up to 24 hours at 2℃ to 30℃ until tested. Remnant specimens will be batch frozen at -80℃, and discarded within 6 months after data collection is complete, according to Good Laboratory Practice (GLP).

Laboratory Testing: Specimens will be tested for NG and CT using Xpert® CT/NG [Cepheid, Sunnyvale, CA] at each of the clinical sites within 24-72 hours of collection by trained technicians. The vaginal swab used for testing is contained in the Cepheid GeneXpert CT/NG Vaginal/Endocervical Specimen Collection kit. Once collected, the study technician will follow the test kit instructions for swab preparation and testing. Xpert provides 90-minute detection and differentiation of CT and NG; it has high sensitivity and specificity[40] and functions well in resource-constrained environments and clinical settings such as those proposed here. All specimens will be run on-site with standard controls, per manufacturer's instructions.Each test includes a sample processing control (SPC) to ensure correct processing of the sample, a sample adequacy control (SAC) which ensures adequate cell lysis for nucleic acid extraction and a probe check control (PCC). The PCC monitors reagent rehydration, reaction-tube filling, probe integrity, and dye stability. Ms. Ebonwu (Co-Investigator) will oversee laboratory training and testing to ensure high quality and reliability of results.

Reporting and Treatment: The Xpert system consists of an instrument, personal computer, and preloaded software for running tests on collected samples and displaying results as either positive or negative. All study participants testing positive for CT or NG will be immediately notified by the study nurse. Clinical staff will provide standard care and treatment per the South African Department of Health's STI treatment protocols.[41,42] Study participants being treated for CT and/or NG will be asked to provide a second vaginal swab specimen 3 weeks after treatment to document treatment outcome. Persistently positive participants will be retreated. Final treatment outcomes will be assessed by collection and testing of post-treatment vaginal swab specimen. Study nurses will record testing results in the patients' clinical file as well as into report forms designed for the study.

All women testing positive for CT and/or NG will be asked to notify their partners and bring them to the clinic for counseling and immediate provision of treatment according to South African STI treatment guidelines. Women will be given the option to allow partner(s) to present to the clinic for treatment, or be given oral medication to take to their partner(s). Women infected with CT will be given oral Azithromycin (two 500 mg tablets). Women infected with GC will be given oral Cefixime (one 400 mg tablet) and oral Azithromycin (two 500 mg tablets). These "partner packets" of medications will be placed inside a small yellow envelope labeled with the medication name, dosage, instructions, expiration date and lot number. Successful partner treatment will be measured by participant self-report. Per South African National Guidelines for HIV rescreening at 32 weeks of pregnancy, all women that test positive for CT and/or NG will be rescreened at week 32. Appointments for rescreening will be scheduled during the test-of-cure follow-up.

Analysis: Acceptability of NG and CT screening at the first ANC visit will be defined as at least 80% of eligible women offered CT/NG testing consenting to testing. Feasibility will be defined as at least 90% of all pregnant women who test positive for CT and/or NG through the pilot screening program provided standard treatment per South African STI Treatment Guidelines[41] and returning for test of cure. Proportions of NG and CT infection in HIV-infected pregnant women will be based on positive PCR test results [# positive/ (# negative + # positive)].Treatment outcomes will be calculated as the proportion of treatment success vs. treatment failure. "No treatment" will be categorized as failure. We will complete a descriptive analysis of the differences between women who are eligible participating, eligible non-participating, and currently pregnant and living with HIV but otherwise ineligible, including sociodemographic information as well as reasons for refusal/ineligibility.

These qualitative measures will be further supported by qualitative data collection, which will occur with both with patients (see draft data collection tool; Appendix 2.D) and providers. Some insights regarding acceptability and feasibility concerns will be gathered from providers during twice-monthly project personnel meetings. To supplement this regular information, providers will be interviewed one-on-one twice during the year-long implementation period. For those who are not comfortable sharing concerns in person, we will make available an anonymous "suggestion box" for providers to provide private feedback related to implementation.

Potential Challenges and Quality Assurance: Loss-to-follow up of participants testing positive for CT or NG, re-infection by untreated partners of infected women, and test turn-around-time (TAT) will likely be the dominant challenges in this study. As part of the study, FPD will leverage existing clinical roving teams and contact tracers to work directly with the clinic-based study nurses to find lost patients and their partners. Clinic and laboratory study personnel at each study site will meet twice monthly to review study enrollment, specimen collection, processing, TAT, data management, and treatment outcomes. Meetings will discuss descriptive study results to date, problems encountered and remedial actions to be taken.

Specific Aim 2: To describe longitudinal birth and infant outcomes for HIV-infected pregnant women screened for CT and NG in their first antenatal care visit compared with those unscreened for CT/NG. Methods and Procedures.

At the time that participants are being enrolled into the study as part of Aim 1 above, 600 additional participants will be enrolled as part of a comparison group in order to achieve Aim 2. Birth outcome data will then be collected from the 600 participants participating in CT/NG screening as part of Aim 1 as well as the 600 women enrolled in the comparison group. Data on birth outcomes will be used to accomplish two subaims: 2(a): To estimate the frequency of poor birth outcomes such as premature rupture of membranes, preterm labor or delivery, and small for gestational age, and their association with CT and NG screening and treatment, and 2(b): To estimate the frequency of HIV MTCT and its association with CT and NG screening and treatment.

Recruitment and Eligibility: The 600 women in the comparison group will be recruited and enrolled similarly to those participants enrolled in Aim 1. Eligibility criteria for the comparison group are identical to those in the screening group (see Aim 1) except in order to fit follow-up times within the confines of the study period, participants in the comparison group will have previously attended their first ANC visit and thus be ineligible for screening, but be at least 4 weeks prior to anticipated delivery. The participating clinics do not have access to ultrasound machines; however, pregnant women may be referred for gestational age estimation via ultrasound if medically indicated, such as in cases of vaginal bleeding, small fundal height based on date of last period, or absence of fetal movements. Per South African guidelines, gestational age will be measured using date of last menstrual period and symphysis-fundal height (SFH). The SFH measurement will be plotted onto the 50thcentile line on the SFH graph, allowing the corresponding gestational age to be read from the graph. ANC medical records will be abstracted for any ultrasound test results in the study population to assess the quality of the gestational age estimated by the standard methods. As with the screening group, patients will be preliminarily screened for eligibility in the comparison group (age $\geq$ 18 years, currently pregnant with documented HIV infection, residing in Tshwane district and intending to stay in Tshwane district through delivery, having previously attended their first ANC visit, and being at least 4 weeks prior to anticipated delivery) via chart review at the time of the visit; those suspected to be eligible will be formally screened during the visit by study nurses. All eligible patients will be invited to participate, and those providing informed consent will be enrolled.

Data Collection: Study staff will collect data on adverse pregnancy events in study participants of both the screening and comparison group through face-to-face interviews with participating women within 2 weeks of delivery and by review of medical records (see draft data collection instrument, Appendix 2B). Staff will collect information on fetal loss, preterm labor, preterm birth, birth weight and small for gestational age status, as well as infant health data including mortality and serious adverse events including hospitalization, respiratory distress and conjunctivitis. Information on other potential confounding variables such as a maternal history of chronic illness (i.e., hypertension, diabetes), other infections during pregnancy (i.e., urinary tract infections, syphilis), antibiotic usage during pregnancy, and pregnancy complications (i.e., premature rupture of membranes, maternal fever, chorioamnionitis, pre-eclampsia) will also be collected. At 7-8 weeks post-delivery, both HIV PCR test results from routine early infant diagnosis (EID) of HIV-exposed infants at six weeks of age and evidence of pneumonia will be accessed via clinic records by the clinic study nurse or other FPD clinical staff with appropriate permission to access patient medical records (see draft data collection instrument, Appendix 2C). Data collection will be reviewed weekly by a study supervisor who will ensure the completeness and validity of the data by comparing participants' reported outcomes with clinic records; discrepancies will be resolved via interview with the birth attendant (midwife or physician).

Retention and Follow-up: To ensure post-delivery follow up, multiple forms of contact information will be collected for all participants at enrollment. To develop and maintain a strong relationship with study participants,

study nurses will check in with each participant during monthly, regular pickup of antiretroviral therapy. 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. Participants who do not return for scheduled ANC or ART visits after enrollment will be actively contacted by both clinic and study staff and encouraged to return for care. All participant charts will be flagged so that study staff will be notified at the time of delivery. Seven days post-delivery study staff will contact participants to schedule an outcomes interview. Up to seven attempts will be made through various contact methods (i.e. text, mobile phone call, home visit) to follow up with participants. Our prior studies have achieved retention rates greater than 98%[38]and similar rates are expected in this study.

Data Analysis: MTCT data analysis will focus on a pooled, estimate of the effect of CT and NG screening and treatment on MTCT of HIV. The individual effects of screening/treatment for each of these infections will be evaluated with respect to the infants' HIV status. Particular focus will be placed on whether HIV-infected mothers who are unscreened for both CT and GC are at higher risk of having HIV-infected infants (non-intervention comparison group). We will analyze birth outcomes with a particular focus on predictors of preterm birth (babies born alive before 37 weeks gestation) with sub-categorization as extremely preterm (<28 weeks), very preterm (28 to 32 weeks), and moderate-to-late preterm (32 to 37 weeks). To control for the differential inclusion criteria between the intervention and comparison groups, we will analyze by ANC visit number at enrollment to assess any impact this has on birth outcomes.

Potential Challenges: Loss-to-follow up for HIV testing of HIV-exposed infants will likely be the main challenge with this Aim. FPD will leverage existing clinical roving teams and contact tracers to work with the clinic-based study nurse to ensure EID testing. It is also possible that deliveries could occur in township settings without a medical birth attendant; after the expected time of delivery, study staff will work to contact participants and will travel to their township to collect birth outcomes if needed. A recent evaluation study found that when coordinated with 6-week immunization visits, infant EID follow-up was >90%[31]; this strategy has since been adopted at all FPD-supported clinics and we expect to meet or exceed this follow-up rate.

C.6. Sample Size Estimations and Statistical Analyses

Sample Size. The sample size for Aim 1 will be 600 women and the sample size for Aim 2 will include 1200 women total (the 600 participants from Aim 1 and an additional 600 participants in the comparison arm). This sample size was chosen based on the regular head count of patients for ANC visits at the participating clinics, as well as the need for sufficient study power. With 600 eligible subjects in Aim 1, we will be able to estimate a CT/NG screening consenting rate of 80% (acceptability) to within a 95% confidence interval of +/- 3.3%. While this is a pilot study not specifically powered to find a difference in MTCT of HIV, with a sample size of 600 per group and using a Fisher's exact test we will have >78% power to detect an absolute difference in MTCT between groups of at least 3% (5% infection in the control group and 2% in the treated group), assuming a two-sided 0.05 level of significance. Based on the pilot study, we expect 120 participants to test positive for CT and/or NG (20% out of 600). A two-sided 95% confidence interval estimate for 90% of these 120 women being treated (feasibility) will have a width of 11.6%. Similarly, a two-sided 95% confidence interval for 80% of the test results report within a week (feasibility) will have a width of 6.6%. The proposed sample size will provide enough precision for valid estimation of these acceptability and feasibility measures.

Statistical analysis. Descriptive statistics including mean, standard deviation, median, inter-quartile range and frequency distribution will be generated for outcome variables as well as provider and patient characteristics. Graphics such as bar charts, box-plots, and histograms will be used to present the data and check for skewness and normality. Transformations of the outcome variables will be explored and performed if needed. For Aim 1, proportions related to acceptability and feasibility and the corresponding 95% confidence intervals will be calculated. For Aim 2, propensity score method (matching, stratification, or weighting) will be used to adjust for possible confounders when evaluating birth outcomes between women with CT and NG screening and treatment and the control group. The first step will utilize a logistic regression with the outcome of group and the covariates such as clinic site, age, pregnancy history, etc. The fitted values from the model are the propensity scores. Next, we will explicitly match the subjects across the groups using a greedy nearest neighbor caliper matching without replacement algorithm.[43] Finally, mixed effects regression models (with a term for the match pair) will be used to compare birth outcomes between groups.

Statistical analysis will include determination of prevalence, adjusted odds ratios, confidence intervals, and multivariate logistic regression. Longitudinal birth outcomes will be described by frequency estimates of single events and multiple events. For all statistical investigations, tests for significance are two-tailed. All analyses will be conducted with Stata 9.0 (Stata Corporation, College Station, TX, 2006).

PROTECTION OF HUMAN SUBJECTS

Involvement of Human Subjects and Their Characteristics

Proposed involvement of human subjects in the work outlined in the Research Strategy section: This study will take place in the Tshwane District, Gauteng Province, South Africa, recruiting participants from the population of pregnant women presenting for ANC services at the two study clinics. Patients will be preliminarily screened for eligibility via chart review at the time of the appointment; all those suspected to be eligible will be formally screened during the visit by study nurses. Current standard of care in South Africa includes *no routine screening* for gonorrhea (NG) or chlamydia (CT) for pregnant women. Though syndromic screening (i.e. screening for symptoms of vaginal discharge) is routine and women with symptoms are managed and treated according to World Health Organization recommendations, the majority of women with NG or CT show no symptoms, and there are no recommendations for routine screening for CT or NG for asymptomatic women in antenatal care settings by either the South African National Department of Health or the World Health Organization.

For Aim 1, 600 eligible participants will be enrolled at the time of first antenatal visit. Eligible participants will be provided with specific information about CT and NG infection, the consequences and treatment of those infections, study risks and benefits, and invited to participate. Those providing informed consent will be enrolled, instructed on how to self-collect a vaginal swab specimen and asked to share several forms of detailed contact information to assure follow-up. Reasons for refusal will be collected whenever possible from eligible women who choose not to enroll. Those testing positive for CT or NG will be asked to notify their partners and bring them to the clinic for counseling and immediate provision of treatment according to existing South African STI treatment guidelines. Per guidelines, women will be given the option to allow partner(s) to present to the clinic for treatment, or be given oral medication to take to their partner(s).

For Aim 2, an additional 600 participants who meet all the eligibility criteria for screening but who have previously attended their first ANC visit and are thus ineligible per Aim 1 will be recruited and enrolled as part of a comparison group in order to provide estimates of the frequency of poor birth outcomes and HIV MTCT. All eligible patients will be invited to participate, and those providing informed consent will be enrolled into the comparison group and asked to share several forms of detailed contact information to assure follow-up post-delivery.

Characteristics of the subject population, including their anticipated number, age range, and health status: All women enrolled in the study (1200 total) will be ≥ age 18 and pregnant, attending ANC visits at one of two clinics in Tshwane District.

Inclusion and exclusion criteria:

For Aims 1 and 2, Eligibility criteria include:

1. Age ≥ 18 years
2. Currently pregnant
3. Documented HIV infection
4. Willingness to self-administer a vulvo-vaginal swab
5. Residence in Tshwane district
6. Intent to stay in Tshwane district through the time of delivery

For Aim 1, Eligibility criteria also include:

1. Attending the first ANC visit for this pregnancy (for intervention group)

Exclusion Criteria:

1. Unable to give informed consent
2. Unlikely to complete study follow-up.

Collaborating sites where human subjects research will be performed. All research will be performed at one of two FPD study clinics in Tshwane District, Pretoria, South Africa: KT Motubatse Clinic, and Soshanguve Community Health Center. Follow-up contact may be made by text, mobile phone call or home visit.

Sources of Material. Research material obtained from living human subjects is as follows: For Aim 1, patients will be preliminarily screened for eligibility via chart review at the time of the appointment and those suspected to be eligible will be formally screened during the visit by study nurses trained in the study methods and human subjects' research using a baseline collection form (see Appendix 2.A). Eligible participants will provide a self-collected vulvo-vaginal swab specimen during their visit, which will be handed to a trained nurse who will label them with a unique study barcode and place them in the secure storage area. Participants testing positive for either CT or NG will receive care and treatment per the South African Department of Health's STI treatment protocols, and a second vaginal swab specimen will be collected 3 weeks after treatment. Sources of material will include patient charts, researcher notes, completed data collection forms, and self-collected swab specimens. Qualitative information related to acceptability and feasibility of self-collected swabs will also be collected from participants after specimen collection is completed, using a data collection tool (see Appendix 2.D) adapted from one currently in use in the region for a cervical cancer screening project.

For Aim 2, patients will be screened as per Aim 1. Sources of material will include patient charts, birth outcome data collection forms (see Appendix 2.B) and researcher notes. For both Aim 1 and Aim 2, an outcomes interview will be performed by study staff 7-14 days post-delivery, using the birth outcome data collection tool. At 7-8 weeks post-delivery, infant HIV PCR results and evidence of neonatal conjunctivitis will be gathered directly from clinic medical records, by clinic nurses or other clinical staff with appropriate permission to access patient medical records, using the Early Infant Diagnosis (EID) Data Collection Tool (see Appendix 2.C).

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. However, as a retention strategy for the post-delivery follow up, participants will be asked to give multiple forms of contact information. 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.

Risks to Participants. The primary potential risks to participants due to study participation are psychological and social in nature. Physical risks from a self-collected vulvo-vaginal swab are negligible. Since screening for CT or NG is not a routine part of the standard of care for pregnant women in South Africa, participants in the comparison group have no risk greater than that normally incurred during a typical antenatal care visit; i.e. mild physical or psychological discomfort.

A. Psychological: Participants could experience psychological distress such as anxiety when discussing issues related to personal experiences. However, we do not expect any serious events to occur based on our experience across multiple previous studies. Participants may experience some stress related to the knowledge of STI status. Participants will be given information and education about the nature and consequences of CT and NG infection and treatment, and those testing positive will be provided treatment as per standard treatment protocols. The likely harmful consequences of learning one's STI status are low.

B. 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.

Alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research. Participants from the target population invited to participate will be able to decline participation, with no consequence to them.

Plans for the recruitment of subjects and the process for obtaining informed consent. The target population will be recruited directly from the population of women presenting for ANC services at the two study clinics in Tshwane District, following chart review for eligibility prior to the visit. Potential participants will be offered the chance to participate by study staff at the time of visit. For Aims 1 and 2, recruited participants will sign a written consent form with study staff before the research activity takes place; this consent form will be approved by the UCLA IRB.

Protection Against Risk. The main risk to the subjects is loss of privacy and psychological distress due to an STI test result. 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.

Potential Benefits to Participants. The potential benefits to subjects include receiving basic information about CT and NG, as well as learning their STI status, which will mean access to early treatment and services if they test positive.

Importance of the Knowledge Being Obtained. This study has the potential to significantly inform programs aimed at the prevention of HIV MTCT in South Africa in the era of Option B policy, and to directly impact clinical and public health practices in low and middle-income countries relating to maternal-child health, especially relating to bacterial STIs. Current standard of care for pregnant women in South Africa does not include CT or NG screening, largely due to the lack of high-level scientific evidence of benefit. If shown to be feasible, acceptable and potentially efficacious, the pilot intervention from this study will serve as a basis for a larger randomized controlled trial in the future, and has the potentially to ultimately lead to an improvement in the standard of care for pregnant women.

IRB Review Procedures to Protect Human Participants. This protocol will be subject to review and approval by institutional review boards at UCLA and FPD. This will include approval prior to the initiation of research, ongoing adverse event monitoring, periodic review, and final study reporting.

Adverse Event Reporting. Although none anticipated, all adverse events will be reported to each IRB.

Data and Safety Monitoring Board. A Data and Safety Monitoring Board is not required nor planned for this study.

INCLUSION OF WOMEN AND MINORITIES

All participants in this study will be African women, by design, since the target population of the study is HIV-infected pregnant women in the Tshwane District, Gauteng Province, South Africa. Therefore 100% of target population participants will be ethnic minorities, and all will be women.

INCLUSION OF CHILDREN

Children (i.e., individuals under the age of 18) are not eligible for participation in this study. The study is designed with a focus specifically on pregnant South African women ages 18 and older, as local data show that teens under 18 have poorer birth outcomes for a variety of reasons, which could confound study results. This restriction is reasonable as most teen pregnancies in South Africa occur in girls 18 and older.

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. 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, and an in-person site visit to South Africa in Years 1 and 2. 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

PIs Klausner and Medina-Marino will lead teams working collaboratively from within the University of California, Los Angeles (UCLA) and the Foundation for Professional Development (FPD) in Pretoria, South Africa.

UCLA will house the contact PI (Jeffrey D. Klausner, MD) and part of the research team, provide the support for the UCLA administrative and IRB components, and oversee study design, methods, data analysis and dissemination efforts. FPD, under the leadership of PI Andrew Medina-Marino, PhD, 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.

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; part of this project will include building capacity for FPD staff to successfully plan and execute this type of research. 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.

Cepheid

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April 6, 2015

Jeffrey D. Klausner, MD, MPH
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9911 W Pico Blvd
Suite # 955
Los Angeles, CA 90035

Andrew Medina-Marino, PhD
Foundation for Professional Development (FPD)
173 Mary Road, The Willows
Pretoria, 0184
South Africa

RE: PA-13-303 / R21

Dear Drs. Klausner and Medina-Marino:

I very enthusiastically write this letter of support for your proposed NIH study, *Pilot Study of STI Screening and Treatment for PMTCT in South Africa*.

Cepheid is dedicated to improving the health of women and children, and preventing HIV. Our Xpert® CT/NG detection system is an on-demand, rapid test that allows for the detection and differentiation of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in low-resource clinical settings. We look forward to working with your research team to ensure that you can provide screening for CT/NG and investigate the impact of these diseases on birth outcomes and HIV mother to child transmission in South Africa. Cepheid is happy to lend two Xpert machines and provide CT/NG cartridges for 600 tests for your pilot study as a donation.

We thank you for the opportunity to continue to collaborate with you in this important work.

Please be in touch if there is anything else we can do.

Sincerely,

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

904 Caribbean Drive Sunnyvale, CA 94089 USA

FPD

April 13, 2015

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)
Lecturer, School of Health Systems and Public Health
University of Pretoria

Re: Letter of Commitment

Dear Drs. Klausner and Medina-Marino:

I enthusiastically write this letter of commitment to serve as a consultant for your proposed NIH study *Pilot Study of STI Screening and Treatment for PMTCT*. I have spent many years as a senior health care manager, improving the South African National TB programme indicators through the successful implementation of both programs and management systems. Your proposal is innovative and fills an important gap in knowledge: the acceptability and feasibility of gonorrhea and chlamydia screening and treatment among HIV-infected pregnancy women in South Africa. This research may result in national policy changes that will have positive effects for the health of mothers and children nationwide.

For the last 15 years I have primarily been focusing on the impact of TB in health care management, and improving the South African National TB programme indicators through streamlined management and improved recording and reporting. As head of FPD's Priority Health Initiatives programme, I am currently managing more than 300 employees from physicians to community health workers at primary care and district level, providing much needed health systems support. In this role I am intensely involved in the assessment and improvement of complex health systems and the implementation of best practices to improve access to and the quality of health services delivery in resource-poor areas of South Africa.

For this study, I will provide support as an Implementation Scientist with extensive experience supervising and managing HIV-related mother and child health programmes. I will commit an average of two hours of consultation per month at the rate of $50 an hour, for an annual total of $1200.00.

I am excited to combine my experience in implementing complicated systems and my expertise in improving the quality of health services delivery in South Africa, in order to support your critical project. I look forward to a fruitful collaboration with you on this study.

Sincerely,

Margot Uys, MB, BCh

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Tshwane District Health Services

HAST Chief Directorate

Enquiries: Mrs DONT Mataboge - Matjebe
Cell no: 0823380103
Tel: 012 451-9154
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e-mail:natalie.matjebe@gauteng.gov.za

To: Dr. Andrew Medina-Marino, PhD

Dr. Jeffrey D. Klausner, MD, MPH

Subject: Research Study Letter of Support

Date: 10 April 2015

RE: RFA-AI-14-010 / R21

Dear Colleagues (Drs. Medina-Marino and Klausner)

I am very excited to learn about your latest proposal to the NIH, titled ***Pilot Study of STI Screening and Treatment for PMTCT in South Africa***.

The pilot study is an important one. It has the potential to lead to a transformation of the state of pregnancy and neonatal outcomes in South Africa, in relation to HIV.

This Study is an effort to determine the following aspects.

- Acceptability and feasibility of screening and treating HIV-infected pregnant women for *Neisseria gonorrhoeae* (NG) *and Chlamydia trachomatis* (CT) at their first antenatal care visit,
- Exploring the impact of these infections on birth outcomes
- Ultimately estimating the frequency of mother-to-child transmission (MTCT) of HIV among women who have been screened for these STIs

I am fully aware that you both have substantial expertise as leaders in HIV and STD prevention and control research and programs, locally in South Africa and internationally.

The Foundation for Professional Development is the leading supporting partners health-systems strengthening in Tshwane and nationally, and we look forward to working closely with you to support the successful implementation of this pilot screening and treatment programme.

If there is anything else I can do to support this work, please do not hesitate to contact me.

Best of luck on your application

Sincerely,

Mataboge-Matjebe

Natalie Octavia Mataboge-Matjebe
Deputy Director: HAST Programme Manager

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April 6, 2015

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)
Lecturer, School of Health Systems and Public Health
University of Pretoria

Re: Letter of Commitment, R21

Dear Drs. Klausner and Medina-Marino:

It is my pleasure to write this letter of commitment to serve as a consultant for your proposed study *Pilot Study of STI Screening and Treatment for* PMTCT, to be funded by the NIH. I have spent many years as an OB-GYN physician-scientist, 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 others in order to improve health for people infected with or affected by HIV, particularly in developing countries. I believe that your proposal to assess the feasibility and acceptability of gonorrhea and chlamydia screening and treatment in HIV-infected pregnant women in South Africa is innovative and critically important, both to the community of the Tshwane District and to the science of public health and HIV PMTCT.

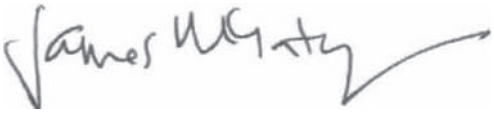
This work is especially important since, as you know, screening for chlamydia and gonorrhea among pregnant women is not the standard of care in South Africa, largely due to the lack of high-level scientific evidence of benefit.

For this study, I will provide support as an OB-GYN with extensive experience conducting research projects on the scale of that proposed here. 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 design and implementation of this pilot study.

I am able to commit an average of two hours of consultation per month, at the rate of $81 an hour, for a total of $1944.00 per year.

I am excited to combine my experience with obstetrics and gynecology with my expertise in PMTVCT, in order to support your project to investigate the feasibility and acceptability of CT and NG screening on HIV-infected pregnant women and examine associated birth outcomes. I look forward to a fruitful collaboration with you on this study.

Sincerely,



Dr. James Mcintyre, MBChB, FRCOG
Executive Director
Anova Health Institute

And
Honorary Professor, School of Public Health & Family Medicine, University of Cape Town

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 Microsoft Access databases and cleaned data along with documentation of variable names, meanings, and codes will be available to any investigators who request such data directly from one of 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 UCLA or FPD before this transfer of data can be made. Datasets will be available 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.

Planned Enrollment Report

Study Title: Pilot Study of STI Screening and Treatment for PMTCT

Domestic/Foreign: Foreign

Comments:

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	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	1200	0	0	0	1200
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	1200	0	0	0	1200

APPENDIX 1: Pregnancy Outcomes - Results from the Data Collection Instrument Used in Pilot Study, Lima, Peru, Nov 2012-May 2013

	N=249	%
Gestational age (median , range)	39	
Deliveries at term	235	94.3
Prematurity (<37 weeks gestation)	14	5.7
Cesarean section	125	50
Maternal complications		
None	196	79
HTN/ preeclampsia	11	4.4
Oligohydramnios	2	0.8
Placenta previa	3	1.2
Nuchal Cord	9	3.6
Premature rupture of membranes	9	3.6
Postpartum hemorrhage	1	0.4
UTI	2	0.8
Cord prolapse	1	0.4
HELLP syndrome	2	0.8
Fetal distress	2	0.8
Hypothyroidism	1	0.4
Abortion	2	0.8
Uterine rupture	1	0.4
Hyperthyroidsm	2	0.8
Venous thrombosis	1	0.4
Hydatid Cyst	1	0.4
Puerperal endometritis	2	0.8
Polyhydramnios	1	0.4
Neonatal Complications		
No complications	197	79.1
Stillbirth	1	0.4
Acute respiratory distress	2	0.8
Malposition	11	4.4
Conjuntivitis	3	1.2
Cyst in CNS	1	0.4
Low birth weight	4	1.6
Macrosomia	23	9.2
Hyperbilirubinemia	5	2
Congenital malformations	2	0.8
Conjoined twin	1	0.4
Clavicular fracture	2	0.8
Intrauterine growth restriction	3	1.2
Fetal bradycardia	2	0.8
Gastroschisis (Congenial malformation)	2	0.8

APPENDIX 2: Data Collection Tools

A. BASELINE PARTICIPANT DATA COLLECTION TOOL

Study No:

Medical record No:

Name of facility:

Date of enrollment: _____/ ____/ _____ (YYYY/MM/DD)

Group: Screening ☐ Comparison ☐

	SOCIO-DEMOGRAPHICS
	Date of birth: _____/ ____/ _____ (YYYY/MM/DD)
	Age (years):
	Ethnic group: African ☐ Coloured ☐ White ☐ Indian ☐ Other ☐
	Employed: Yes ☐ No ☐
	Type of work: Professional ☐ Business ☐ House wife ☐
	Level of Education: None ☐ Below matric ☐ Matric ☐ Tertiary ☐
	Marital status: Married ☐ Single ☐ Divorced ☐
	First pregnancy: Yes ☐ No ☐
	Number of previous pregnancies:
	SOCIO-BEHAVIOURAL CHARACTERISTICS
	Age at first sexual intercourse (years):
	New sex partner in past 3 months: Yes ☐ No ☐
	Multiple sex partners in past 12 months: Yes ☐ No ☐
	Alcohol use: Yes ☐ No ☐
	Illicit drug use: Yes ☐ No ☐

	Condom use: Never ☐ Sometimes ☐ Always ☐
	Commercial sex work: Yes ☐ No ☐
	Frequency of going to clubs/parties: Never ☐ Sometimes ☐ Always ☐
	Frequency of going to movies: Never ☐ Sometimes ☐ Always ☐
CLINICAL INFORMATION	
	Gestational age (weeks):
	Symphasis-Fundal Height (cm):
	Date of first day of last period:
	Period data: Reliable ☐ Approximate ☐ Unknown☐
	HIV viral load:
	CD4 count:
	ART treatment: Yes ☐ No ☐
	Have you ever had an STD? Yes ☐ No ☐
	Were you treated? Yes ☐ No ☐
	Have any of your partners had STD? Yes ☐ No ☐ Not sure ☐
	Did partner obtain treatment? Yes ☐ No ☐ Not sure ☐
KNOWLEDGE AND ATTITUDE	
	Apart from HIV, have you heard of other diseases that men and women can catch by having sexual intercourse? Yes ☐ No ☐
	Have you ever heard of Gonorrhoea? Yes ☐ No ☐
	Have you ever heard of Chlamydia? Yes ☐ No ☐
	Are they curable? Yes ☐ No ☐
	Have you heard of mother to child prevention? Yes ☐ No ☐
	Do you know the effect of HIV on pregnancy? Yes ☐ No ☐

	Do you know the effect of Gonorrhoea on pregnancy? Yes ☐ No ☐
	Do you know the effect of Chlamydia on pregnancy? Yes ☐ No ☐
	Do you know these effects can be prevented? Yes ☐ No ☐
	Do you know that screening and treatment of gonorrhoea and Chlamydia can prevent adverse pregnancy outcomes? Yes ☐ No ☐
	Have you heard of partner notification? Yes ☐ No ☐
CONTACT DETAILS	
	Residential address:
	Cell number:
	Land Telephone number:
	Email address:
	Contact number of relative or friend (1):
	Contact number of relative or friend (2):

B: BIRTH OUTCOME DATA COLLECTION TOOL

Study No:

Medical record No:

Name of facility:

Date of enrollment: _____/ ____/ _____ (YYYY/MM/DD)

Group: Screening ☐ Comparison ☐

	MATERNAL CHARACTERISTICS
	Is the mother alive: Yes ☐ No ☐
	Mode of delivery: Vaginal ☐ Caesarean ☐ Other ☐
	Place of delivery: Clinic ☐ Home ☐ other ☐
	Number of Ante-natal care visits:
	History of adverse pregnancy outcome: Yes ☐ No ☐
	History of chronic illness: None ☐ Hypertension ☐ Diabetes ☐ Other ☐
	Other infections during pregnancy: None ☐ Urinary tract infection ☐ Syphilis ☐ Other ☐
	Antibiotic usage during pregnancy: Yes ☐ No ☐
	Maternal complications: None ☐ Premature rupture of membranes ☐ Preeclampsia ☐ Maternal fever ☐ Premature labour ☐

	Postpartum haemorrhage ☐ Chorioamnionitis ☐ Other ☐
	Adverse birth outcomes: None ☐ Premature birth ☐ Still birth ☐ Other ☐
	Premature birth: Extremely preterm ☐ Very preterm ☐ Moderate preterm ☐
PERINATAL CHARACTERISTICS	
	Was baby born alive?: Yes ☐ No ☐
	Gestational age at birth (weeks):
	Weight at birth (kilograms):
	HIV PCR test result: Positive ☐ Negative ☐
	Perinatal complications: None ☐ Low birth weight ☐ Acute respiratory distress ☐ Conjunctivitis ☐ Congenital malformations ☐ Other ☐

Definitions:

Premature Birth: Baby born alive before 37 weeks of gestation with sub categorisation as extremely preterm (<28 weeks), very preterm (28 to 32 weeks) and moderately preterm (33 to 37 weeks).

Premature Labour: Onset of labour in the preterm period (<37 weeks).

Preterm Rupture of Membranes: Leakage of amniotic fluid during the preterm period (<37 weeks) caused by the rupture of the foetal membranes.

Stillbirth: Baby born with no signs of life at or after 28 weeks' gestation.

C: EARLY INFANT DIAGNOSIS (EID) DATA COLLECTION TOOL

Study No:

Medical record No:

Name of facility:

Date of enrollment: _____/ ____/ _____ (YYYY/MM/DD)

Group: Screening ☐ Comparison ☐

Date of delivery: _____/ ____/ _____ (YYYY/MM/DD)

Date of chart review: _____/ ____/ _____ (YYYY/MM/DD) *(should be 7-8 weeks from delivery)*

CHART REVIEW RESULTS	
	Date of HIV PCR test: _____/ ____/ _____ (YYYY/MM/DD)
	HIV PCR test result: Positive ☐ Negative ☐
	Evidence of Chlamydia pneumonia: Yes ☐ No ☐

D: POST-SCREENING QUESTIONNAIRE

Women's Experiences with Self-Collection of Vaginal Swab

We would now like to ask you some questions about the self-collection of a vaginal swab you just performed. The purpose of these questions is to gain knowledge from women about their experiences with self-collecting a specimen for screening for STIs. Your answers to these questions are confidential and will not affect your care here. It is very important for research purposes that you be open and honest in your answers. Your answers will help us provide the best care for women like you.

1. **How were the directions to self-collect a vaginal swab given to you?**
    a. Directions were given to me verbally only
    b. Directions were given to me in written format only
    c. Directions were given to me both verbally and in written format
    d. Refused/ No Answer

2. **In what language did you receive instructions on specimen collection?**
    a. Directions were given to me in my mother tongue
    b. Directions were given in a language I understand well
    c. Directions were given in a language I understand poorly
    d. Refused/ No Answer

3. **How well did the instructions prepare you to perform the self-collection?**
    a. They prepared me well – I had no further questions
    b. They prepared not so well – I had a number of questions
    c. They prepared me poorly – I still had many questions
    d. They did not prepare me well at all – I required assistance doing the test

    If the participant answered A, skip to question 5

4. **Would any of the following items have prepared you better to self-collect a specimen? Please circle all that apply.**
    a. More detailed pictures
    b. Better verbal instructions
    c. A demonstration video
    d. None of the above
    e. I don't know

Interviewer: you will now be asking questions regarding the study participant's experience with performing the self-collection

5. **Were you provided with a private space to self-collect a vaginal swab?**
    1. Yes
    2. No

    If "NO," please describe what about the space was not private.

6. **On a scale from 1 to 10, with 1 being very clean and 10 being very dirty, how clean was the space where you self-collected your specimen? Please circle one.**

Very Clean	1	2	3	4	5	6	7	8	9	10	Very Dirty

If the study participant responded with 7, 8, 9, or 10, please have them describe the state of the space provided.

7. **On a scale from 1 to 10, with 1 being very comfortable and 10 being very uncomfortable, how comfortable was the space where you self-collected your specimen? Please circle one.**

Very Comfortable	1	2	3	4	5	6	7	8	9	10	Very Uncomfortable

If the study participant responded with 7, 8, 9, or 10, please have them describe the state of the space provided.

8. **On a scale from 1 to 10, with 1 being very easy and 10 being very difficult, how easy was it for you to self-collect a vaginal swab? Please circle one.**

Very Easy	1	2	3	4	5	6	7	8	9	10	Very Difficult

If the study participant responded with 7, 8, 9, or 10, please have them describe what about the self-collect process was not easy.

9. **On a scale from 1 to 10, with 1 being no discomfort and 10 being severe discomfort, did inserting and swabbing the inside of your vagina cause any physical discomfort? Please circle one.**

No Discomfort	1	2	3	4	5	6	7	8	9	10	Severe Discomfort

If the study participant responded with 7, 8, 9, or 10, please have them describe what about the insertion or swabbing caused discomfort.

10. **From the time that you were given a swab to when you collected your specimen, how long did it take?**
    a. Less than 5 minutes
    b. 5-10 minutes
    c. More than 10 minutes, but less than 20 minutes
    d. More than 20 minutes, but less than 30 minutes
    e. More than 30 minutes

11. **Would you be willing to be screened again before your baby is born?**
    a. Yes
    b. No

12. **Your being in this study will help the South African government determine if and how all pregnant women in South Africa should self-collect specimens for STI screening during pregnancy.**
    Please give us suggestions how we might make the experience better:

_____

_____

_____

_____

Thank you for taking the time to answer my questions.

Proposal Summary

Proposal Number: PAR 13-303 **Proposal Status:**
Sponsor Deadline: 05/07/2015 **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:	10833 Le Conte Ave.	**Street2:**	CHS 13-154
City:	Los Angeles	**County:**	Los Angeles County
State:	CA	**Zip Code:**	90095-1725
Country:	USA	**Employee ID:**	
Phone:	310-267-0409	**Fax:**	310-825-3157
Email:	JDKlausner@mednet.ucla.edu		

First Budget Period Effort: **Calendar:** 1.20 **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: NIH Exploratory/Developmental Research Grant Program (Parent R21)
Sponsor Type:
Sponsor Code:
Sponsor Name:
SubDivision 1:
SubDivision 2:

PROJECT DATA

Title of Project: Pilot Study of STI Screening and Treatment for PMTCT
Is This a Subcontract?
If Yes, who is prime?
Type of Proposal:
Type of Agency:
Kind of Application: Resubmission
Previous Grant # or Federal Identifier: HD084274
Change in grantee institution? No
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

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:	09/01/2015	08/31/2016
Cumulative Budget Period:	09/01/2015	08/31/2017

Cost Sharing Information	Mandatory	Voluntary
Committed:		
Amount:		
Source:		

Budget Period	Direct Cost	Indirect Cost	Total Cost
Period 1:	131,250	38,810	170,060
Period 2:	158,169	25,858	184,027
Total:	289,419	64,668	354,087

AWARD DATA

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

Budget Period	Direct Cost	Indirect Cost	Total Cost
Period 1:			
Period 2:			
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:

FOUNDATION FOR PROFESSIONAL DEVELOPMENT (PTY) LTD

COST APPLICATION : 24 MONTHS

DETAIL BUDGET FOR PROJECT NIH

TOTAL ZAR and US$ *10.20*

	TOTAL : YEAR 1	TOTAL : YEAR 2	TOTAL RAND FUNDING	TOTAL US$ FUNDING	% of Total Budget
PROJECT	R 796,921	R 1,041,567	R 1,838,488	$180,244	95%
	R 796,921	R 1,041,567	R 1,838,488	$180,244	
OPERATIONS	R 40,760	R 54,562	R 95,322	$9,345	5%
SUPPORT AND IMPLEMENTATION SERVICES	R 40,760	R 54,562	R 95,322	$9,345	
TOTALS PER ZAR	R 837,681	R 1,096,128	R 1,933,810	$189,589	100%
TOTALS PER USD	*$82,126*	*$107,464*	*$189,589*		
	$78,129	*$102,114*			

THE TOP-TEN INVESTIGATOR RESPONSIBILITIES

UCLA DEPARTMENT OF MEDICINE
CLINICAL RESEARCH

As Principal Investigator, you are responsible for making sure that the following occur:

1. A **prospective** review and approval of all human subject research protocols by the UCLA IRB (or certification of exemption).
   - *IRB approval is required for all human subject research before it can start.*
   - *If there is a lapse in the annual renewal, research must be put on hold until an up-to-date approval is provided by the IRB.*
2. An investigator named on the IRB-stamped consent form provides and documents the process of written informed consent.
   - *Responsibility for the consent process cannot be delegated to a nurse or coordinator.*
   - *An investigator cannot sign-off on consent that was obtained by others.*
   - *A named investigator must personally assure that the subject understands what is described in the consent, their alternative options, the risks, and that they may revoke their consent at any time without jeopardizing their care.*
3. Subjects receive a copy of the IRB-stamped informed consent, the State of California Subject's Bill of Rights (for medical research), and the IRB-approved HIPAA Research Authorization form (when applicable) as part of the consent process.
   - *Subjects must get a copy of all of their signed consent documents.*
   - *You must retain a signed copy of all documents with your study records.*
4. Study visits and procedures are carried out exactly as described in the IRB-approved consent forms and any proposed changes to the protocol are **prospectively** submitted to the IRB for review and approval. The only exception is when changes are needed to eliminate an immediate hazard to the subject.
   - *No changes to the study procedures, investigators, or protocols are allowed without first submitting them to the IRB and obtaining IRB approval.*
   - *Additional studies/tests, the collection/storage of additional samples, or changes in drug administration may not be implemented without IRB review and approval.*
5. Protocol violations/deviations are reported to the IRB, as well as any injuries or unanticipated problems involving risks to human subjects.
   - *Anything that is not "working" with the study should be reported to the IRB along with suggestions for changes/corrections.*
6. Good clinical practice guidelines are followed when performing clinical research.
   - *Maintain source documents for all visits, procedures and tests in order to provide independent verification of the information recorded on the case report forms.*
   - *Maintain a comprehensive regulatory binder that includes copies of all correspondence with the IRB, FDA and sponsor, as well as protocols and amendments, etc.*
   - *All tests used for clinical decision-making must be performed in CLIA-certified laboratories or in a similarly certified manner.*

- *All study drugs and investigational agents must be maintained and dispensed by the Investigational Drug Section (IDS) of the Ronald Reagan UCLA Medical Center Department of Pharmaceutical Services according to an approved pharmacy protocol.*
- *All information recorded onto the case report form will be reviewed by a study investigator, with documentation of approval or corrective action for abnormal values and/or protocol violations. You are directly responsible for the integrity of the study data and the safety of the subjects.*

7. Serious adverse events are immediately reported according to the UCLA IRB Decision Tree for internal or external events and FDA guidelines.
   - *Report first – obtain and report follow-up details later.*
   - *It does not always matter if the SAE is related to the study, it must be immediately reported if required by the UCLA IRB Decision Tree guidelines.*
8. All of the investigators/staff involved in human subject research are knowledgeable of the research protocol and IRB polices and appropriately trained and/or certified for the research that they are conducting including Human Research Subject Protection, HIPAA, blood drawing, biosafety, sample shipping, etc.
   - *You should personally verify certificates of training.*
   - *Offer additional training to your staff when their responsibilities increase.*
   - *Foreign-trained physicians that lack a valid California medical license may not perform medical procedures, medical evaluations or in any way act in the role of a treating physician.*
9. The privacy and confidentiality of personally identifiable information for all human subjects participating in research is maintained, except as required by law or if release of this information is requested in writing by the subject.
   - *No personal identifiers should appear on case report forms.*
10. All aspects of research funding and expenditures are handled in a manner consistent with University and/or funding agency guidelines.
    - *Limit and supervise all petty cash distributions.*
    - *Meet regularly with fund managers to review expenditures.*

The opportunity to carry out research involving human subjects is an honor and a privilege that carries with it a number of responsibilities. As the Principal Investigator, you will be responsible for these Top-Ten responsibilities as well as many others that are mandated by the University, the funding agency, the FDA, the IRB, University Contracts and Grants, and the Department.

I have read these responsibilities and agree to apply them to my research study entitled:
Pilot Study of STI Screening and Treatment for PMTCT Resubmission

Sponsor Name NIH

Signature	Print Name	Date
	Jeffrey D. Klausner MD, MPH	04/24/2015

Department of Medicine
Other Support Summary
Jeffrey D. Klausner, M.D.

ALL **ACTIVE** CONTRACT & GRANTS (Include clinical trials)

Line #	Agency Name & Grant Number	Dates of Funding	Total Current Effort	Total Adjusted Effort if proposals are funded
1	UPCH R01 Award	8/1/13-7/31/17	8%	8%
2	UPCH Supplement	8/1/14-7/31/15	10.0%	0.0%
3	R21 Drug Resistant Gonorrhea (NIH)	08/15/2014-07/31/2016	15%	15%
4	R01 TB in Botswana-Upenn/NIH/NIAID	9/1/13-8/31/16	5%	5%
5	R25 Fogarty	07/01/14-06/30/15	3.5%	3.5%
6	STI-CTG-SSS/NIH	9/15/14-9/14/15	25%	0%
8	ARLG - DOD Anatomic Testing Protocol Subcontract	1/1/15-11/30/15	10%	10%
		Total **ACTIVE** Research Effort:	76%	41%

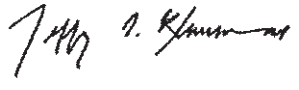
ALL **PENDING** CONTRACT & GRANTS PROPOSALS (Include this grant proposal submission)

Line #	Agency Name & Grant Number	Dates of Funding	Total Effort on original proposal budget	Total Adjusted Effort if proposals are funded
1	PAR 13-303 R21 with FPD Resubmission	09/01/2015-08/31/2017	10%	10%
2	R01 Self Testing in AA Men Resubmission	09/01/2015-08/31/2019	30%	22%
3	UPCH DOD	04/01/2015-03/31/2016	5%	5%
4	STI-CTG-SSS/NIH 29k Supplement	04/01/2015-12/31/2015	7%	7%
5	DOD - Anatomic Testing Protocol Subcontract	01/01/2015-12/31/2015	5%	5%
		Total **PENDING** Research Effort:	57%	49%

GRAND TOTAL ACTIVE & PENDING RESEARCH EFFORT: 90%

Comments (Please justify any grand total over 85%):

Dr. Klausner is pending an approval from the Dean's office for 90% effort.

Signature of PI:  **Date:** 4/24/2015

Signature of Fund Manager:  **Date:** 4/24/2015

Request [redacted] Exception [redacted] Policy 900 / Principal Investigator [redacted]

[redacted] process [redacted] exception [illegible] Policy [redacted]

Name: Jeffrey D. Klausner, MD MPH   Current Academic [redacted] Clinical Professor

Department: Medicine – Infectious Diseases   [redacted] Address: jdklausner@mednet.ucla.edu

Campus Address: 10833 LeConte Avenue Los Angeles, CA 90095 CHS 13-15[illegible]

[redacted] Supervisor/Mentor: Thomas J. Coates, PhD
[redacted] individual [redacted] supervision [illegible] another [illegible] please [illegible] supervisor [redacted]

Campus Phone: [illegible]   Campus [redacted] 310-825-3157

[redacted] individual [redacted] Principal Investigator [redacted] Co-Principal Investigator

[redacted] exception applies [redacted] project

Specific Project: PAR-13-303

Proposal Title: *Pilot Study of STI Screening and Treatment for [illegible] Resubmission*

Agency: NIH

[redacted] Investigators/Co-PIs:

Project Number [illegible] available): [illegible]   [redacted] Proposal Submitted/Due: [illegible]

[redacted] justify [illegible] request [illegible] exception (attach additional [illegible] necessary):
[redacted] Division [illegible] Infectious Diseases, [redacted] request [redacted] exception [redacted] Policy [redacted] Jeffrey Klausner, [illegible] MPH, [redacted] Principal Investigator [redacted] project referenced [redacted] Interest [illegible] Division [illegible] Infectious Diseases. [redacted] Klausner [redacted] Principal Investigator, [redacted] capable [illegible] conducting [redacted] research projects. Ample space [redacted] facilities, [redacted] administrative support [illegible] available [redacted] pursue [redacted] research under [redacted] pertaining [redacted] project. [redacted] support [redacted] endorse [redacted] research.

Requested [illegible] *Division Chief*

[redacted] [illegible], MD   ______________________ (Signature)   [illegible]

Dean [illegible] PhD   ______________________ (Signature)   [illegible]

[redacted]   ______________________ (Signature)
[redacted] [illegible] APPENDIX [illegible]

APPROVED: ______________________

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	D	Klausner	604207032	jdklausner@mednet.ucla.edu	310-267-0409
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-ID/CARE FS Code (Dept. Code): 1560

Account #: 441344 Cost Center: JK Recharge ID: YIPE

Dept. Contact Name: Kristine Mariscal Extension: 66186 Email Address: kmariscal@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: Pilot Study of STI Screening and Treatment for PMTCT

Project Begin Date: 09/01/2015 Project End Date: 08/31/2017

4. **Award/Proposal/Program Type**

Award Type: Grant Proposal Type: Resubmission New

Program Type: Basic 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

Sponsor Due Date: 05/07/2015 Time (Pacific): 5PM

Deadline Type: Electronic

FOA/RFA/RFP# (*if applicable*): PA13-303

Contact (*if known*):

Email Address: Phone #:

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

Prime Sponsor Name:

Prime Sponsor Due Date: Time (Pacific):

Prime FOA/RFA/RFP# (*if different*):

6. **Proposal Checklist**

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 10833 Le Conte Ave. Los Angeles, CA 90095 Room: CHS 13-154
☐	☑	Off Campus Space? Indicate location:
☑	☐	Outgoing Agreements? If yes, provide entity names in Section 9, Remarks, and attach Sub-recipient Commitment Form(s) for each entity. PI signature below indicates review and approval of cost reasonableness. (See Subaward Initiation and Management)
☑	☐	Does this project involve activities outside the U.S. or partnership with International Collaborators?
☐	☑	Is any Cost Sharing/Matching proposed in this application? (Do not include unfunded effort or salary cap differential here.) If Yes, required by sponsor? ☐ Yes (mandatory committed) ☐ No (voluntary committed) Cost Share Amount: Source/FAU#:
☐	☑	Is any unfunded effort proposed in this application? (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" or IRB#: Pending Delayed Onset ☐
☐	☑	Are study related patient care costs to be billed to the award OR to a third party payor (i.e. medical insurance/Medicare)? If yes, then a Policy 915 Coverage Analysis is required (refer to www.clinicaltrials.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:
☐	☑	Biological materials? For more information, see Biological Safety Division 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: 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 Administration Office Checklist to determine additional required attachments.

8. Funds Requested

1st Budget Period

Direct Costs ($): 125,000 Excluded Direct Costs ($): 59,379 F&A Costs ($): 38,810 Total Costs ($): 170,060

All Project Periods (*complete only when multiple budget periods are involved*)

Direct Costs ($): 275,000 Excluded Direct Costs ($): 169,662 F&A Costs ($): 64,668 Total Costs ($): 354,087

F&A

F&A Rate (%): 54 F&A Base Type: MTDC If Other, specify:

9. Remarks

Submitted via DOM DRA and consortium institution Foundation for Professional Development (Pty) Ltd

10. Accepts Responsibility

Approvals: Includes Certifications

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. When multiple Investigators are proposed in an application this assurance must be obtained by all named Investigators.

Principal Investigator (Required)	4/29/15 Date	Chair/ORU Director/Dean/Medical Center Director (Required)	4/29/15 Date
Other	Date		Date
CAO	Date		Date

For proposal submissions prior to August 24, 2012, funded by **Federal Public Health Service (PHS)** or an agency that has adopted **the PHS regulations**, attach COI **Form 740 & Supplement to Form 740** (if applicable). Effective August 24, 2012 in lieu of filing the 740(s), complete the information below for all project personnel responsible for the design, conduct, or reporting of research. To access the web-based disclosure system, go to **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	For ORA Use Only
Jeffrey	D	Klausner	jdklausner@mednet.ucla.edu	05/13/2014
Xiaoyan		Wang	xywang@mednet.ucla.edu	06/08/2014

PI: Klausner, Jeffrey	YEAR 1	YEAR 2	TOTAL
DIRECT COSTS (UCLA DC + SUBAWARDS DC):	125,000	150,000	275,001
SUBAWARD F&A:	6,250	8,169	14,419
TOTAL DIRECT COSTS:	131,250	158,169	289,420
UCLA F&A BASE:	71,871	47,886	119,758
F&A RATE:	54%	54%	
F&A:	38,811	25,859	64,670
TOTAL COSTS:	**170,061**	**184,028**	**354,090**

Exclusions from F&A base:

	YEAR 1	YEAR 2	TOTAL
Space Rental Costs:	-	-	-
GSR Remission Fees:	-	-	-
Subaward (see details below)	59,379	110,283	169,662
Equipment:	-	-	-
Subtotal	**59,379**	**110,283**	**169,662**

Target numbers for staying within $500,000/year

Subawards - populate totals here:

Subaward Direct Costs	YEAR 1	YEAR 2	TOTAL
Subaward #1: FPD	78,129	102,114	180,243
Subaward #2	-	-	-
Subaward #3	-	-	-
Subaward #4	-	-	-
Subaward #5	-	-	-
Total Subaward Direct Costs	**78,129**	**102,114**	**180,243**
Subaward F&A Costs			
Subaward #1: FPD	6,250	8,169	14,419
Subaward #2	-	-	-
Subaward #3	-	-	-
Subaward #4	-	-	-
Subaward #5	-	-	-
Total Subaward F&A Costs	**6,250**	**8,169**	**14,419**
Subaward Total Costs			
Subaward #1: FPD	84,379	110,283	194,662
Subaward #2	-	-	-
Subaward #3	-	-	-
Subaward #4	-	-	-
Subaward #5	-	-	-
Total Subaward Total Costs	**84,379**	**110,283**	**194,662**
Subaward Costs Allocated to IDC Base*	Total per subaward line should NOT exceed $25,000		
Subaward #1: FPD	25,000	-	25,000
Subaward #2	-	-	-
Subaward #3	-	-	-
Subaward #4	-	-	-
Subaward #5	-	-	-
Total Subaward Costs Allocated to IDC Base	**25,000**	**-**	**25,000**

*Only 1st $25,000 is subject to MTDC F&A. Enter up to $25,000 for the each subward according to the yearly budget.

RESTRICTIONS per FOA 13-303
DC max for two years $275k, but no more than $200k per year DC requests in modules of $25k

University of California, Los Angeles
Office of Contract and Grant Administration ATTACHMENT B

SUBRECIPIENT COMMITMENT FORM

All subrecipients should complete this form when submitting a proposal to UCLA. It provides a checklist of documents and certifications required by sponsors, as well as an area for the authorized institutional representative to sign.

SUBRECIPIENT'S LEGAL NAME: Foundation for Professional Development (Pty) Ltd

SUBRECIPIENT'S PI: Andrew Medina-Marino

UCLA's PI: Jeffrey Klausner PRIME SPONSOR: NIH

UCLA's PROPOSAL TITLE: Pilot Study of STI Screening and Treatment for PMTCT

SUBRECIPIENT'S TOTAL FUNDS REQUESTED: 194,662

SUBRECIPIENT'S PERFORMANCE PERIOD: BEGIN: 09/01/2015 END: 08/31/2017

SECTION A - Proposal Documents

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) completed & signed by subrecipient authorized institutional representative (required)*

SECTION B - Certifications

1. **Facilities and Administrative Rates** included in this proposal have been calculated based on:

   ☒ Our federally-negotiated F&A rates for this type of work, or a reduced F&A rate that we hereby agree to accept. *(if this box is checked, a copy of your F&A rate agreement must be furnished to UCLA via hard copy, website, or email before a subaward will be issued.)*

   ☐ Other rates *(please specify the basis on which the rate has been calculated in Section E Comments below)*

   ☐ Not applicable *(no indirect cost request for subrecipient)*

2. **Fringe Benefit Rates** included in this proposal have been calculated based on:

   ☐ Rates consistent with or lower than our federally-negotiated rates *(if this box is checked, a copy of your Fringe Benefit rate agreement must be furnished to UCLA before a subaward will be issued).*

   ☒ Other rates *(please specify the basis on which the rate has been calculated in Section E Comments below)*

3. **Human Subjects** ☐ **Yes** ☒ **No**
   (If "Yes": Copies of the IRB approval and approved "Informed Consent" form must be provided before any subaward will be issued. Please forward these documents to UCLA's PI as soon as they become available. This is required before any subaward will be issued.)

   ***If "Yes" and NIH funding is involved*: Have all key personnel involved completed Human Subjects Training?** ☐ **Yes** ☐ **No**

   Note: All key personnel engaged in human subject research must take the NIH human subjects training or human subject research training (http://grants.nih.gov/grants/policy/hs_educ_faq.htm)

4. **Animal Subjects** ☐ **Yes** ☒ **No**
   (If "Yes": A copy of the IACUC approval must be provided before any subaward will be issued. Please forward this document to UCLA's PI as soon as it becomes available. This is required 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 this document to UCLA's PI as soon as it becomes available. This is required before any subaward will be issued.)

6. **Conflict of Interest (applicable to NSF, NSF flow-throughs 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 financial disclosure.

☐ Subrecipient Organization/Institution hereby certifies that it has an active and enforced conflict of interest policy that is consistent with the provision of 42 CFR Part 50, Subpart F "Responsibility of Applicants for Promoting Objectivity in Research." Subrecipient also certifies that, to the best of Institution's knowledge, (1) all financial disclosures have been made related to the activities that may be funded by or through a resulting agreement, and required by its conflict of interest policy; and, (2) all identified conflicts of interest have or will have been satisfactorily managed, reduced or eliminated in accordance with subrecipient's conflict of interest policy prior to the expenditures of any funds under any resultant agreement.

☒ Subrecipient does not have an active and/or enforced conflict of interest policy and hereby agrees to abide by UCLA's policy and related procedures. See http://www.adminpolicies.ucla.edu/app/Default.aspx?&id=925-3 for the text of UCLA's policy.

7. **Conflict of Interest for Public Health Service** (applicable to projects funded by PHS/NIH, or other programs requiring disclosure under PHS rules. FPD does not provide a Public Health Service.

☐ My organization **DOES HAVE** a PHS-compliant Financial Conflict of Interest (FCOI) policy and my organization will rely on this policy and associated procedures to comply with the PHS Conflict of Interest regulation.

☐ Yes, we are registered as an organization with a PHS-compliant FCOI policy with the FDP Clearinghouse.

☐ 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 who are responsible for the design, conduct, or reporting of the research.

See: PHS Financial Disclosure form

Attach PHS Disclosure of Financial Conflict of Interest Form for each individual named below.

	Disclosure of FCOI Form Attached
Subrecipient PI Name: Andrew Medina-Marino	☐
Investigator: Joy Ebonwu	☐
Investigator: Study Nurse (TBA)	☐
Investigator:	☐
Investigator:	☐

8. **Cost Sharing/Matching/In-Kind** ☐ **Yes** ☒ **No** **Amount:** _____
(Cost sharing, Matching, and/or In-Kind amounts and justification should be included in the subrecipient's budget).

9. **Certification Regarding Debarment and Suspension**
Is the entity, PI or any other employee or student participating in this project debarred, suspended or otherwise excluded from or ineligible for participation in federal department, agency, assistance programs or activities?

☐ **Yes** ☒ **No** *(If "yes", explain in Section E Comments below.)*

Subawards to any entity or individual included in the Federal excluded Parties are prohibited.

10. **Ethics in Research Training (applicable to projects funded by NSF)**
☒ Not applicable because this project is not being funded by NSF.
☐ 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.

11. **Is subrecipient a for-profit entity?** ☒ **Yes** ☐ **No**
If yes, UCLA PI should complete Fair and Reasonable Cost Analysis form (Attachment AA) located at: http://www.research.ucla.edu/ocga/Forms/reasonable_interactive.pdf and attach it to this form.

SECTION C - Audit Status

1. **A-133 Audit Status** http://www.whitehouse.gov/sites/default/files/omb/assets/omb/circulars/a133/a133.pdf

FPD has an A-21 Audit annually. Exit Conference for 2013 audit is scheduled for 23 September 2014

☒ Subrecipient DOES receive an annual audit in accordance with OMB Circular A-133.
Most recent fiscal year completed: FY 2012

☐ **Yes** ☒ **No** Were there any audit findings reported? (If "Yes," explain in Section E, *Comments*, below)

Note: A complete copy of subrecipient's most recent audit report or the Internet URL link to a complete copy, must be furnished to University of California, Los Angeles before a subaward will be issued.

☐ Subrecipient DOES NOT receive an annual audit in accordance with OMB Circular A-133.
Subrecipient is a:
☐ Non-profit entity (under federal funding threshold)
☐ Foreign entity
☒ For-profit entity
☐ Government entity

Note: If a subrecipient does not receive an A-133 audit, UCLA will require the entity to complete an Audit Certification and Financial Status Questionnaire, prior to establishment of a subaward:
http://www.research.ucla.edu/ocga/Forms/a-133_interactive.pdf

When applying for funds from agencies under the U.S. Department of Health and Human Services foreign organizations and for-profits that have expended a total of $500,000 or more under one or more awards from the U.S. Department of Health and Human Services (as a direct grantee and/or under a consortium participant) will be required to have a financial-related audit of all HHS awards as defined in, and in accordance with, the Government Auditing Standards or an audit that meets the requirement of OMB Circular A-133.

SECTION D - Federal Funding Accountability and Transparency Act (FFATA)

1. Location of Subrecipient (Name, Address, City, State, Zip + 4, Congressional District, and Country):

Foundation for Professional Development (Pty) Ltd, Struland Office Park, 173 Mary F

Note: If primary place of performance is different than Location of Subrecipient, provide location of where the project will be performed (Name, Address, City, State, Zip +4, Congressional District, and Country)

2. DUNS Number (+ 4) of Subrecipient receiving award:

568904572

3. Is Subrecipient owned or controlled by a parent entity? ☒ Yes ☐ No

NOTE: If yes, please provide the Name, DUNS Number (+ 4), and Location (Address, City, State, Zip + 4, Congressional District, and Country) of parent entity:

Parent entity does not receive funds from foreign government, as such does not hav

4. Does Subrecipient currently have an active registration in the System for Award Management (www.sam.gov)?
☒ Yes ☐ No

NOTE: Organizations that have not registered with SAM will need to obtain a DUNS number first and then access the SAM online registration through SAM home page at https://www.sam.gov.
Subrecipients must be registered and maintain their current information in SAM.

5. Exempt from reporting compensation ☐ Yes ☒ No If no, proceed with filling out the top 5 paid officers below. Executive compensation information for the Subrecipient must be reported if: More than 80% of annual gross revenues are from the Federal government, and those revenues are greater than $25M annually; compensation information is nor already available through reporting to the Security & Exchange Commission (SEC).

Officer 1	Name	Gustaaf Wolvaardt	Compensation	US$ 223,529
Officer 2	Name	Veena Pillay	Compensation	US$ 126,023
Officer 3	Name	Suzanne Johnson	Compensation	US$ 126,023
Officer 4	Name	Margot Uys	Compensation	US$ 120,092
Officer 5	Name	Nkhensani Nkhwas	Compensation	US$ 120,092

6. **Project Description:** In compliance with our FFATA reporting obligations, please provide a succinct (no more than 4000 characters) description of the overall purpose and expected outcomes. This information will be displayed on the http://USAspending.gov website and available to the general public.

The current proposed study will help fill critical gaps in the understanding of how bacterial STIs may impact MTCT of HIV infection in the era of combination ART in pregnant women. Given the high prevalence of HIV infected pregnant women in South Africa (over 300,000 HIV-infected women deliver annually17)and the high prevalence of STIs in women of reproductive age, South Africa provides an ideal setting to understand these multifaceted, overlooked interactions. At present, little is known about the ways in which bacterial STIs in pregnancy may impact MTCT of HIV. An enhanced, comprehensive understanding of risk factors for HIV MTCT is essential, particularly in South Africa with its high prevalence of co-infection. Currently, prenatal screening for bacterial STIs is not routinely conducted in low and middle-income countries around the world. While South African policy stipulates that pregnant women are to be screened for HIV and syphilis during their first ANC visit, routine antenatal screening is not conducted for CT or NG. Studies such as this one may help enhance our understanding of the prevalence, impact and attributable risk of CT and/or NG infections and MTCT of HIV. Furthermore, given the known adverse consequences of CT and NG on maternal-child health outcomes, this study may be

SECTION E - Comments

FPD's Facilities and Administrative Rates are based on internal policies. FPD's Fringe Benefits Rates are also based on internal policies.

APPROVED FOR SUBRECIPIENT:

The information, certifications and representations above have been read, signed and made by an authorized official of the subrecipient named herein. The appropriate programmatic and administrative personnel involved in this application are aware of agency policy 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 Official)	Struland Office Park, 173 Mary Road, The Willc (Address)
Gustaaf George Wolvaardt (Type or print name and title of Authorized Official)	Pretoria, Gauteng, South Africa (City, State, Zip)
Foundation for Professional Deve (Name and EIN of Subrecipient Organization/Institution)	+27 12 816 9000 (Phone) +27 86 567 025 (FAX)
4 May 2015 (Date)	development@foundation.co.za (Email)