File No. 120095 Committee Item No. _____
Board Item No. 36

COMMITTEE/BOARD OF SUPERVISORS

AGENDA PACKET CONTENTS LIST

Board of Supervisors Meeting **Date** February 7, 2012

Cmte	Board	
☐	☐	**Motion**
☐	☒	**Resolution**
☐	☐	**Ordinance**
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☐	☐	**Budget Analyst Report**
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☐	☒	**Award Letter**
☐	☒	**Application**
☐	☐	**Public Correspondence**

OTHER **(Use back side if additional space is needed)**

☐	☐	_____
☐	☐	_____
☐	☐	_____
☐	☐	_____
☐	☐	_____

Completed by: Andrea Ausberry **Date** February 2, 2012
Completed by: _____ **Date** _____

An asterisked item represents the cover sheet to a document that exceeds 25 pages.
The complete document is in the file.

FILE NO. 120095 RESOLUTION NO.

[Accept and Expend Grant - Tuberculosis Epidemiologic Studies - $23,538]

Resolution authorizing the Department of Public Health to retroactively accept and expend a grant in the amount of $23,538 from the California Department of Public Health, to participate in a program entitled Tuberculosis Epidemiologic Studies Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection" for the period of November 1, 2011, through September 28, 2012, and waiving indirect costs.

WHEREAS, California Department of Public Health is the recipient of a grant award from the Centers for Disease Control and Prevention supporting the Tuberculosis Epidemiologic Studies (TBESC) Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection"; and,

WHEREAS, With a portion of these funds, California Department of Public Health has subcontracted with San Francisco Department of Public Health (DPH) in the amount of $23,538 for the period of November 1, 2011 through September 28, 2012; and,

WHEREAS, The full project period of the grant starts on November 1, 2011 and ends on September 14, 2021, with years two, three, four, five, six, seven, eight, nine and ten subject to availability of funds and satisfactory progress of the project; and,

WHEREAS, As a condition of receiving the grant funds, California Department of Public Health requires the City to enter into an agreement (the "Agreement"), a copy of which is on file with the Clerk of the Board of Supervisors in File No.120095; which is hereby declared to be a part of this resolution as if set forth fully herein; and,

WHEREAS, The purpose of this project is to improve the diagnosis and treatment of latent TB infection (LTBI) in the United States; and,

WHEREAS, An Annual Salary Ordinance amendment is not required as the grant partially reimburses DPH for two existing positions, one Registered Nurse (Job Class No. 2320) at .1 FTE and one Epidemiologist I (Job Class No. 2802) at .05 FTE, for the period of November 1, 2011, through September 28, 2012; and,

WHEREAS, A request for retroactive approval is being sought because DPH did not receive notification of the revised award until November 2, 2011 for a project start date of November 1, 2011; and,

WHEREAS, Tuberculosis Epidemiologic Studies (TBESC) Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection" grant does not contain indirect costs because California Department of Public Health prohibits including indirect costs in the budget; and

WHEREAS, The grant terms prohibit including indirect costs in the grant budget; now, therefore, be it

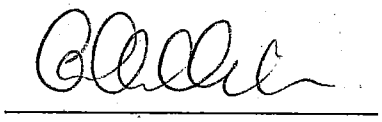
RESOLVED, That DPH is hereby authorized to accept and expend a grant retroactively in the amount of $23,538 from California Department of Public Health; and, be it

FURTHER RESOLVED, That the Board of Supervisors hereby waives inclusion of indirect costs in the grant budget; and, be it

FURTHER RESOLVED, That DPH is hereby authorized to retroactively accept and expend the grant funds pursuant to San Francisco Administrative Code section 10.170-1; and, be it

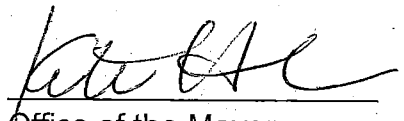
FURTHER RESOLVED, That the Director of Health is authorized to enter into the agreement on behalf of the City.

RECOMMENDED:

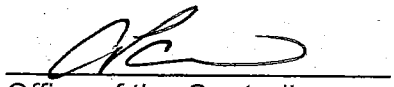


Barbara A. Garcia, MPA
Director of Health

APPROVED:



Office of the Mayor



Office of the Controller

City and County of San Francisco

Department of Public Health

Edwin M. Lee
Mayor

Barbara A. Garcia, MPA
Director of Health

TO: Angela Calvillo, Clerk of the Board of Supervisors

FROM: Barbara A. Garcia, MPA
Director of Health

DATE: November 18, 2011

SUBJECT: Grant Accept and Expend

GRANT TITLE: Tuberculosis Epidemiologic Studies Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection" - $23,538

Attached please find the original and 4 copies of each of the following:

☒ Proposed grant resolution, original signed by Department

☒ Grant information form, including disability checklist -

☒ Budget and Budget Justification

☒ Grant application:

☒ Agreement / Award Letter

☐ Other (Explain):

Special Timeline Requirements:

Departmental representative to receive a copy of the adopted resolution:

Name: Richelle-Lynn Mojica Phone: 255-3555

Interoffice Mail Address: Dept. of Public Health, Office of Quality Management for Community Programs, 1380 Howard St.

Certified copy required Yes ☐ No ☒

(415) 554-2600 101 Grove Street San Francisco, CA 94102-4593

File Number: 120095
(Provided by Clerk of Board of Supervisors)

Grant Information Form
(Effective March 2005)

Purpose: Accompanies proposed Board of Supervisors resolutions authorizing a Department to accept and expend grant funds.

The following describes the grant referred to in the accompanying resolution:

1. Grant Title: **Tuberculosis Epidemiologic Studies (TBESC) Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection"**

2. Department: **Department of Public Health, Tuberculosis Control Section**

3. Contact Person: **Jennifer Grinsdale (Program Manager)** Telephone: **415.206.6101**

4. Grant Approval Status (check one):

[X] Approved by funding agency [ ] Not yet approved

5. Amount of Grant Funding Approved or Applied for:

$ 23,538 year 1*
$ 227,360 year 2
$ 231,301 year 3
$ 235,267 year 4
$ 241,396 year 5
$ 245,959 year 6
$ 252,395 year 7
$ 257,746 year 8
$ 167,466 year 9
$ 121,050 year 10

Total for project: $2,003,475

DPH is seeking accept and expend approval for year 1 only. The funding agency will approve subsequent years upon successful completion of the prior year. DPH will include these years in the DPH budget.

6a. Matching Funds Required: **No**
b. Source(s) of matching funds (if applicable): **N/A**

7a. Grant Source Agency: **Centers for Disease Control and Prevention, Division of TB Elimination**
b. Grant Pass-Through Agency (if applicable): **CA Dept. of Public Health, Tuberculosis Control Branch**

8. Proposed Grant Project Summary: **The objective of the TBESC, Task Order 1, "Improving the Diagnosis and Treatment of Latent TB Infection", is to improve the diagnosis and treatment of latent TB infection (LTBI) in the United States. Activities in this study include evaluating: (1) Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRAs) in diagnosing LTBI and predicting progression from LTBI to TB disease; and (2) measures to enhance adherence to, and completion of,**

LTBI treatment. Successful completion of this project will provide valuable information needed to ensure widespread adoption of the best practice methods for TB screening and prevention.

9. Grant Project Schedule, as allowed in approval documents, or as proposed:

Year 1	Start-Date: **November 1, 2011**	End-Date: **September 28, 2012**
Year 2	Start-Date: **September 29, 2012**	End-Date: **September 14, 2013**
Year 3	Start-Date: **September 15, 2013**	End-Date: **September 14, 2014**
Year 4	Start-Date: **September 15, 2014**	End-Date: **September 14, 2015**
Year 5	Start-Date: **September 15, 2015**	End-Date: **September 14, 2016**
Year 6	Start-Date: **September 15, 2016**	End-Date: **September 14, 2017**
Year 7	Start-Date: **September 15, 2017**	End-Date: **September 14, 2018**
Year 8	Start-Date: **September 15, 2018**	End-Date: **September 14, 2019**
Year 9	Start-Date: **September 15, 2019**	End-Date: **September 14, 2020**
Year 10	Start-Date: **September 15, 2020**	End-Date: **September 14, 2021**
Total Project Period:	Start-Date: **November 1, 2011**	End-Date: **September 14, 2021**

10a. Amount budgeted for contractual services: **$0**

b. Will contractual services be put out to bid? **N/A**

c. If so, will contract services help to further the goals of the department's MBE/WBE requirements? **N/A**

d. Is this likely to be a one-time or ongoing request for contracting out? **N/A**

11a. Does the budget include indirect costs? [ ] Yes [X] No

b1. If yes, how much? **N/A**
b2. How was the amount calculated? **N/A**

c. If no, why are indirect costs not included?
[X] Not allowed by granting agency [ ] To maximize use of grant funds on direct services
[ ] Other (please explain):

12. Any other significant grant requirements or comments:
Department of Public Health respectfully request for approval to accept and expend these funds retroactive to November 1, 2011. The Department received the revised award letter on November 2, 2011.

GRANT CODE (Please include Grant Code and Detail in FAMIS): **HCDC12**

****Disability Access Checklist*****

13. This Grant is intended for activities at (check all that apply):

[X] Existing Site(s) [X] Existing Structure(s) [X] Existing Program(s) or Service(s)
[ ] Rehabilitated Site(s) [ ] Rehabilitated Structure(s) [ ] New Program(s) or Service(s)
[ ] New Site(s) [ ] New Structure(s)

14. The Departmental ADA Coordinator and/or the Mayor's Office on Disability have reviewed the proposal and concluded that the project as proposed will be in compliance with the Americans with Disabilities Act and all other Federal, State and local access laws and regulations and will allow the full inclusion of persons with disabilities, or will require unreasonable hardship exceptions, as described in the comments section:

Comments:

Departmental or Mayor's Office of Disability Reviewer: _____ Jason Hashimoto

Date Reviewed: 11/18/11

Department Approval: _____ Director of Public Health

Barbara A. Garcia, MPA
(Signature)

San Francisco Department of Public Health, TB Control Se n: Tuberculosis Epidemiologic Studies Task Order 1

Budget

Detail Description for Contractor by Activity

(Year 1)

(11/1/11 through 9/28/12)

Description	FTE	Annual Salary	Major Functions, Services and Activities						Total Cost
			B.1.	1.1	1.2	1.3	1.4	1.5	
Personnel									
In-kind									
Site Principal Investigator (M. Kawamura)	10%	$195,000	$9,750	$975	$1,950	$975	$3,900	$1,950	$19,500
Fringe Benefits @ 24.1%			$2,350	$235	$470	$235	$940	$470	$4,700
Total In-kind			$12,100	$1,210	$2,420	$1,210	$4,840	$2,420	$24,200
Epidemiologist I	5%	$72,259	$1,806		$1,112		$417	$278	$3,613
Research Nurse (6 months)	20%	$96,668		$2,835	$2,835	$558	$3,114	$325	$9,667
Fringe Benefits @ 35%			$632	$992	$1,381	$195	$1,236	$211	$4,647
Total Personnel & Fringe Benefits			$2,439	$3,827	$5,328	$753	$4,767	$814	$17,928
Operating Expenses									
Quantiferon TB Gold In-tube - 25 x $35 per test				$875					$875
Incentives - 25 patients x $25 each				$1,250					$1,250
General Office supplies - $50 per month x 6 months				$300					$300
Clinic supplies - $50 per month x 6 months				$300					$300
Shipping costs - 1 container x $50 x 2 shipments				$100					$100
Printing forms: 15 x 50 copies @ .07 each				$53					$53
Language line services - $50 per month x 6 months				$150					$150
Total Operating Expenses			$0	$3,028	$0	$0	$0	$0	$3,028
Out-of-State Travel									$1,500
1 trip x 1 person x $930 Roundtrip airfare				$930					
3 days per diem x $40/day x 1 person x 1 trip				$120					
2 nights lodging @ $150/night x 1 person x 1 trip				$300					
1 car rental x 3 days x $50/day				$150					
In-State Travel							$1,083		$1,083
75 miles/wk x 26 weeks x $0.555/mile									
TOTAL BUDGET			**$2,439**	**$6,855**	**$5,328**	**$753**	**$5,850**	**$814**	**$23,538**

Funded by the Centers for Disease Control and Prevention through the California Department of Public Health

November 1, 2011 - September 14, 2021

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Total
Start Date:	**11/1/2011**	**9/29/2011**	**9/15/2013**	**9/15/2014**	**9/15/2015**	**9/15/2016**	**9/15/2017**	**9/15/2018**	**9/15/2019**	**9/15/2020**	**11/1/2011**
End Date:	**9/28/2012**	**9/14/2013**	**9/14/2014**	**9/14/2015**	**9/14/2016**	**9/14/2017**	**9/15/2018**	**9/14/2019**	**9/14/2020**	**9/14/2021**	**9/14/2001**
Personnel											
The Epidemiologist with review CDC developed study protocol, provide suggestions, modifications and improvements to protocol and review feasibility and practicality as it pertains to clinic services; will be responsible for data collection and analysis including upload of data to CDC and preparing monthly CDC cumulative summary forms; will collect and provide cost-related data according to study protocol. The Reserach RN will be responsible for recruitment, obtaining informed consent, enrollment, data/specimen collection, TST placement and reading, follow-up and referrals for study subjects; will make recommendations to CDC PI to modify study forms/processes/procedures as necessary; will complete study forms as required.											
Epidemiologist I (2802)	$ 3,613	$ 36,130	$ 36,130	$ 36,130	$ 37,394	$ 37,394	$ 38,703	$ 38,703	$ 23,222	$ 23,222	**$ 310,641**
FTE	5%	50%	50%	50%	50%	50%	50%	50%	30%	30%	
Research Nurse (2320)	$ 9,667	$ 99,736	$ 102,830	$ 105,768	$ 109,044	$ 112,424	$ 115,882	$ 119,496	$ 92,430	$ 63,492	**$ 930,769**
FTE	10%	100%	100%	100%	100%	100%	100%	100%	70%	50%	
Fringe											
@ 35%	$ 4,647	$ 47,553	$ 48,636	$ 49,664	$ 51,253	$ 52,436	$ 54,105	$ 55,370	$ 40,478	$ 30,350	**$ 434,492**
Total Personnel and Fringe	*$ 17,927*	*$ 183,419*	*$ 187,596*	*$ 191,562*	*$ 197,691*	*$ 202,254*	*$ 208,690*	*$ 213,569*	*$ 156,130*	*$ 117,064*	*$ 1,675,902*
Supplies											
Computers will be used to facilitate communication with staff and other external entities, to maintain and analyze TB related data, develop reports and presentations and for other mission critical needs. QFT-IT TB blood test kits will be used to test for latent TB infection according to study protocol. Patients will be given incentives at each study visit in the amount of $25 per visit. General office supplies will be used by staff to carry out daily program activities. Clinic supplies will be used when drawing blood from study patients. Shipping costs will be used to mail samples from each of the jurisdictions to the central serum bank. Incentives will be used when enrolling patients and at the end-of-treatment blood draw. General printing will be used to duplicate study protocols, data forms, study material and reference materials. Translation/interpreter services for non-English speaking patients will be provided by Language Line Services.											
Computer Supplies		$ 1,500	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	**$ 1,500**
QFT-IT Tests	$ 875	$ 18,970	$ 20,720	$ 20,720	$ 20,720	$ 20,720	$ 20,720	$ 20,720	$ -	$ -	**$ 144,165**
Incentives	$ 1,250	$ 11,875	$ 13,125	$ 13,125	$ 13,125	$ 13,125	$ 13,125	$ 13,125	$ 5,625	$ -	**$ 97,500**
Office supplies	$ 300	$ 2,400	$ 2,400	$ 2,400	$ 2,400	$ 2,400	$ 2,400	$ 2,400	$ 1,800	$ 1,800	**$ 20,700**
Clinic supplies	$ 300	$ 3,000	$ 3,000	$ 3,000	$ 3,000	$ 3,000	$ 3,000	$ 3,000	$ 300	$ -	**$ 21,600**
Shipping	$ 100	$ 1,200	$ 1,200	$ 1,200	$ 1,200	$ 1,200	$ 1,200	$ 1,200	$ 600	$ -	**$ 9,100**
Cell Phone	$ -	$ 480	$ 480	$ 480	$ 480	$ 480	$ 480	$ 480	$ 480	$ 480	**$ 4,320**
Reproduction	$ 53	$ 315	$ 315	$ 315	$ 315	$ 315	$ 315	$ 788	$ 788	$ 263	**$ 3,781**
Languange services	$ 150	$ 300	$ 300	$ 300	$ 300	$ 300	$ 300	$ 300	$ 300	$ -	**$ 2,550**
Total Supplies	*$ 3,028*	*$ 40,040*	*$ 41,540*	*$ 41,540*	*$ 41,540*	*$ 41,540*	*$ 41,540*	*$ 42,013*	*$ 9,893*	*$ 2,543*	*$ 305,216*

Funded by the Centers for Disease Control and Preven... through the California Department of Public Health

November 1, 2011 - September 14, 2021

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Total
Start Date:	11/1/2011	9/29/2011	9/15/2013	9/15/2014	9/15/2015	9/15/2016	9/15/2017	9/15/2018	9/15/2019	9/15/2020	11/1/2011
End Date:	9/28/2012	9/14/2013	9/14/2014	9/14/2015	9/14/2016	9/14/2017	9/15/2018	9/14/2019	9/14/2020	9/14/2021	9/14/2001
Travel											
Local travel to clinic sites, patient's homes, etc. for follow-up and study oversight. TB Control Program Manager will attend the TBESC kick-off meetining in Atlanta, GA during the first year and the Research RN will attend TBESC training in Atlanta, GA during the second study year.											
Local travel	$ 1,083	$ 2,165	$ 2,165	$ 2,165	$ 2,165	$ 2,165	$ 2,165	$ 2,165	$ 1,443	$ 1,443	**$ 19,121**
Out of state travel	$ 1,500	$ 1,737	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	**$ 3,237**
Total Travel	*$ 2,583*	*$ 3,901*	*$ 2,165*	*$ 2,165*	*$ 2,165*	*$ 2,165*	*$ 2,165*	*$ 2,165*	*$ 1,443*	*$ 1,443*	*$ 22,357*
Total	**$ 23,538**	**$ 227,360**	**$ 231,301**	**$ 235,267**	**$ 241,396**	**$ 245,959**	**$ 252,395**	**$ 257,746**	**$ 167,466**	**$ 121,050**	**$ 2,003,475**

State of California—Health and Human Services Agency
California Department of Public Health

RON CHAPMAN, MD, MPH
Director

EDMUND G. BROWN JR.
Governor

COVER PAGE

REQUEST FOR TASK ORDER PROPOSAL

TECHNICAL PROPOSAL

Request for Proposal
Solicitation number 2011-N-13311, Tuberculosis Epidemiologic Studies Consortium
"Prospective Comparison of the Tuberculin Skin Test (TST) vs. Interferon Gamma Release Assay (IGRAs) in Diagnosing Latent Tuberculosis Infection (LTBI) and in Predicting Progression from LTBI to Active Tuberculosis Disease"

Offeror:
California Department of Public Health
DUNS number 799150615

This document is a(n): ☐ **Original**
☐ **Copy**

Centers for Disease Control and Prevention: Solicitation 2011-N-13311

REQUEST FOR TASK ORDER PROPOSAL

TECHNICAL PROPOSAL

Tuberculosis Epidemiologic Studies Consortium
Request for Proposal
Prospective Comparison of the Tuberculin Skin Test (TST) vs. Interferon Gamma Release Assay (IGRAs) in Diagnosing Latent Tuberculosis Infection (LTBI) and in Predicting Progression from LTBI to Active Tuberculosis Disease

Submitted June 15, 2011

Offeror: California Department of Public Health

Authorized representative:

James Watt, MD, MPH, Chief
Division of Communicable Disease Control
California Department of Public Health

_____
James Watt, MD, MPH

850 Marina Bay Parkway
Richmond, CA 94804
Telephone: (510) 620-3784
Fax: (916) 440-5678
Email: James.Watt@cdph.ca.gov

Authorized to negotiate on the behalf of the offeror:
Jennifer Flood, MD, MPH, Chief
Tuberculosis Control Branch
Division of Communicable Disease Control
California Department of Public Health
Telephone: (510) 620-3020
Fax: (510) 602-3030
Email: Jennifer.Flood@cdph.ca.gov

This proposal reflects our estimates and/or actual costs as of this date and conforms with the instructions set forth in FAR 15.403-5(b)(1) and FAR 15-2. By submitting this proposal, the offeror, if selected for discussions, grants to Contracting Officer or an authorized representative the right to examine, at any time prior to award, any of those books, records, documents, or other records directly pertinent to the information requested or submitted.

TABLE OF CONTENTS

I. UNDERSTANDING THE PROBLEM

A. Need and significance of the research project and its objectives

A public health challenge for the 21st century is the elimination of tuberculosis (TB), which is responsible for an estimated 1.7 million deaths per year across the globe. In the United States (U.S.), successful strategies have been implemented to decrease the burden of TB since the disease's resurgence in the late 1980s and early 1990s. However, in order to reach elimination, in addition to identifying and treating persons with active TB disease, TB control efforts must focus on reducing the large reservoir of potential future active TB cases among persons with latent tuberculosis infection (LTBI)[1,2], a population estimated to be 11 million persons residing in the U.S. and 2.3 million in California[3].

Because the vast majority of persons with LTBI will not progress to active disease, and, in the setting of declining cases of active TB and recent and accumulating cuts to the TB control infrastructure at local, state and national levels, it is crucial to use the most cost-effective testing strategies to identify those persons most likely to progress to active TB disease. Currently, TB control programs use tuberculin skin tests (TST) and/or interferon gamma release assays (IGRAs) combined with the presence of risk factors for progression to disease to determine who should be tested and who should be treated for LTBI. The TST has been well-studied and there is more than a century of experience with its use, but it has major drawbacks of being nonspecific, especially among BCG vaccinated populations; insensitive particularly among immunosuppressed persons; and requires two clinic visits to obtain test results. Although IGRAs, which are more specific and only require a single blood draw to obtain results, seem likely to be an important new tool to identify LTBI and determine who needs treatment to prevent TB, there are many unanswered questions about IGRA implementation. These unanswered questions are addressed in this project's objectives and study questions. Accomplishing the project's objectives of comparing the accuracy and cost-effectiveness of TST and IGRAs in identifying persons with LTBI and predicting who will progress to TB disease would encourage widespread adoption of the best method to prevent active TB and will help enable TB elimination.

The study's primary objectives are important because research to date has not provided definitive answers to several questions including the performance of IGRA among a variety of subgroups, the predictive value of IGRAs for progression to active TB, and the cost-effectiveness of IGRA vs. TST in all high-risk populations. Compared with the TST, IGRAs are expected to have increased specificity because the antigens used are absent in bacillus Calmette-Guérin (BCG) vaccine strains and most environmental mycobacteria. There is no gold standard for diagnosing LTBI because no diagnostic test directly measures the presence of viable tubercle bacilli in persons with latent infection. Studies of sensitivity have generally used populations with diagnoses of active TB disease and compared TST and IGRA results, but the definition of active disease has differed across studies. Although a recent meta-analysis that pooled data only from studies where active TB disease was confirmed demonstrated increased sensitivity of IGRAs compared to TST[4], questions remain about the sensitivity of each IGRA. At the least, IGRAs have similar sensitivity to TST[5]. Studies of specificity generally use populations at very low risk for TB infection and in whom a positive test is likely to be a false positive. However, some "false positives" might be true infection from unrecognized risk. A major strength of the proposed study is that it will enroll patients in the United States who are identified through typical screening programs. Additionally, as a prospective cohort study, progression to

active disease will be determined, providing a metric to assess prevention effectiveness in the high-risk populations studied. These strengths will allow study findings to be readily applied to improve TB control and clinical practice.

The crux of this study is determining the best predictors of progression to active TB. A few recent studies have attempted to address this question, with conflicting findings. A study of immigrant close contacts to infectious TB cases in the Netherlands revealed that the predictive values of QFT-GIT, TB-Spot and TST were comparable[6]. A study of contacts to infectious TB cases in Germany revealed that 13% of QFT-GIT-positive contacts developed active TB disease during a 4-year follow-up period, whereas only 3% of TST (+) (> 5 mm induration) contacts did, suggesting that QFT-GIT was more sensitive than TST in predicting active TB disease[7]. On the other hand, studies of ELISPOT in contacts to infectious TB cases in high burden countries revealed that both ELISPOT-positive and ELISPOT-negative contacts developed active TB disease following identification of LTBI[8,9], revealing that these IGRAs applied to these populations resulted in unacceptably high numbers of false-negatives. One reason for these conflicting findings may be the increased opportunity for TB re-infection during the study follow-up period in the Gambia and Senegal compared to that in Germany. Further work is needed to validate the ability of IGRAs to predict progression to disease among a variety of populations, and the project's objectives will accomplish that goal.

Because risk of progression is increased among those who have medical conditions, such as HIV infection (5-15% annual risk of progression), diabetes mellitus, chronic renal failure, some cancers, previous history of inadequately treated TB, and treatment with immunosuppressive drugs[10], these groups should be tested for LTBI and treated if positive. However, particularly among the immunosuppressed, conflicting evidence exists regarding the performance of IGRA and TST for identifying LTBI. Determining the performance of IGRA vs TST is also particularly important among children who have a high rate of progression to active disease if infected. Among BCG-vaccinated children, the potential benefit of IGRA over TST is especially high, and data on the specificity of IGRAs in this population is encouraging[11], but definitive data remains lacking. Because risk of progression from LTBI to active disease is elevated in these populations, determining the best testing strategy for these groups is critical to TB disease prevention efforts.

B. Understanding of contract requirements and tasks described in the Statement of Work

To accomplish the study objectives, the California study site will perform all requirements listed in the Statement of Work (SOW) and those that will be specified in the study protocol. These activities will include recruiting persons at high risk for LTBI for enrollment into the study, obtaining both TST and QFT-GIT quantitative and qualitative results (QFT-GIT obtained first), determining whether the subject has no TB infection, LTBI, or active TB disease, following persons with LTBI every 6 months for 2 years, regardless of treatment status, treating persons who accept treatment for LTBI with a CDC approved regimen, including following those persons for adverse events during treatment, obtaining a second IGRA at the time treatment would be completed (whether treatment is actually accepted or not), and collecting a blood sample and preparing a serum specimen for freezing and quarterly shipment to CDC for all persons diagnosed with LTBI. Additionally, the study site will record, data-enter, and transmit all data needed for the study including clinical, demographic, diagnostic, outcome, and cost data. The study site will perform all activities with appropriate quality assurance checks, and in compliance with local and national institutional review board requirements. Investigators will be actively

involved in the analysis, interpretation and dissemination of the results of the study and in other activities of the consortium.

II. TECHNICAL APPROACH

Overview

The California Department of Public Health (CDPH) TB Control Branch is the lead agency in the state of California responsible for TB control. California reports the largest number of tuberculosis cases in the nation and has an estimated 3 million residents with latent TB infection. CDPH TB Control Branch provides oversight, funding, and technical assistance for TB control efforts of 61 jurisdictions in California. We propose to contribute to an effective national research consortium by carrying out studies in collaboration with three local TB control programs in California and their associated clinics. These programs are located in San Diego, Orange, and San Francisco. Within San Diego and Orange respectively, the University of California San Diego (UCSD) Owen HIV Clinic and the Orange County Health Care Agency (OCHCA) HIV Clinic will serve as additional research partners. The CDPH Principal Investigator Dr. Jennifer Flood, Project Director Dr. Lisa Pascopella, and Project Coordinator Katya Salcedo will function as a central team providing coordination across study personnel located at each participating clinic. At each local program, the TB controllers, Drs. Masae Kawamura, Kathleen Moser and Julie Low, who each represent nationally recognized TB experts, will be designated as study co-Investigators. In addition, Dr. Richard Garfein and Dr. Constance Benson, are designated co-Investigators for the UCSD Owen HIV Clinic. Each of the three local sites will be staffed with a study nurse (Research Nurse Coordinator) who will oversee, recruit, and enroll study patients. This research nurse will function as the local site coordinator. Local site data management and tracking of enrollment and patients during follow-up will be supported by additional epidemiology and research assistant personnel funded at each local site.

In each of the three sites, the Research Nurse Coordinator will work during clinic hours to approach and enroll patients. Back up will be provided by other study personnel and the site investigator. Clinic staff will be trained on study eligibility to stimulate and assist with flagging and referrals during clinic hours. Regular re-education and re-stimulation for ongoing study recruitment will occur. Study personnel will carry a cell phone for easy and continuous access. Patients will be screened with IGRA and tuberculin skin test (TST) per protocol. TB symptom review, physical exam, and chest radiograph will be performed to exclude active TB. Culture will be performed if the chest radiograph is abnormal or if the patient is symptomatic and HIV-infected. Patients with an LTBI diagnosis will be identified and approached first by the treating physician or nurse. They will be referred for further information and consent by the study nurse, when patients will be fully informed of the study, undergo voluntary consent, and offered incentives. Daily recruitment will occur at all participating California clinics. A procedure manual which provides a step by step process for identification, screening, and enrollment will be developed based upon the finalized study protocol. This procedure manual will detail steps for each participating California clinic. Tracking of enrollment will occur on a daily basis by study staff located in each site and data entry into the central database will occur. Coordination across sites including data merging and analysis, quality assurance, ensuring consistent and efficient protocol implementation and training will be directed by the central Project Coordinator and Project Director. IRB submission and renewal will be managed by the central Project Coordinator and all sites will use the central CDC deferral mechanism with the exception of UCSD. The CDPH TBCB PI, Project Director and Project Coordinator will participate in all aspects of the consortium including committees and will facilitate input and opportunities for direct participation by co-Investigators at each step from finalized protocol input to publications.

Our proposal documents a strong state TB control program with successful past performance in the current TBESC and in multiple additional research initiatives relevant to the new focus of this consortium. The CDPH TB Control program proposes to contribute to a productive national research consortium by carrying out studies in collaboration with California's local TB control programs located in San Diego, Orange, and San Francisco. Each TB controller of these programs brings extensive local and multi-site research experience. The TB clinics under direction of these controllers have been the setting for numerous past TBESC and TB Clinical Trial's Consortium (TBTC) studies and have contributed substantially to study recruitment. The three collaborating programs represent TB control jurisdictions with high TB morbidity and together contribute 22% of the state's total TB case load. In 2009, the total case count for all three jurisdictions combined was 535, which exceeds that case count of most U.S. states for that year. As a TBESC member, the California site will bring to the consortium the ability to recruit a large number of study subjects from diverse settings and populations which include key special populations. Relevant target populations to be enrolled in studies from this California site include children, persons infected with human immunodeficiency virus (HIV), new arrivers, recent contacts to infectious TB patients, patients with abnormal chest radiographs indicative of inactive TB, and key populations from specific countries of origin underrepresented in other parts of the nation. The clinic sites combined have a patient population of over 22,000, with more than 5,000 high risk patients diagnosed with LTBI each year. Of the over 5,000 potential patients eligible for recruitment, this site proposes to enroll 1,500 patients each year as study subjects.

A major strength of our proposal is our ability to enroll a large number of patients at high risk of LTBI, 1500 per year, and to follow and retain study participants with LTBI in the context of TB clinic operations with proven success in patient retention and completion of treatment for LTBI. Additional strengths are our access and ability: 1) to enroll large numbers of the special high risk groups, including at least 800 new arrivers (< 2 years) from countries with high TB incidence, 600 close contacts to infectious TB cases, 500 children younger than 14 years, 300 homeless persons, 300 HIV-infected persons, in addition to persons defined locally as having an increased incidence of LTBI (foreign-born living in U.S. > 2 years), per year; and 2) to follow and retain study participants with LTBI using innovative approaches, such as video directly observed therapy, provision of incentives and enablers, linguistic and culturally matched case managers, educational interventions and accessible clinic hours and home visits, and use of systematic tracking methods. The extensive research experience of CDPH TBCB, San Francisco, San Diego, Orange, and UC San Diego investigators in clinical trials and TBESC studies as well as original research, demonstrates our capacity for successful participation in a research consortium from concept through research translation.

A. Appropriateness of study sites. Describe catchment area and the number of high-risk LTBI patients by population characteristic eligible to be enrolled during study period

The California Department of Public Health Tuberculosis Control Branch will work with the San Francisco, Orange, and San Diego County TB control programs. Together these three California counties reported 23% of the 2329 TB cases reported in California during 2010. Each TB program site is integrated with its TB clinic(s), where the TB controller has direct authority over patient care and clinic processes. All sites have active LTBI testing and treatments programs and together have access to at least 22,000 eligible patients at high risk for LTBI and at least 5,000 patients with LTBI per year. Each site will enroll 250 LTBI patients per year, in addition to 250 patients at high risk of LTBI but without evidence of TB infection, for a total annual

enrollment target of 500 from their TB, refugee and HIV clinics- reaching a total enrollment of 1500 annually in the catchment area. The San Diego site will enroll patients from its TB and refugee clinics, as well as collaborate with the University of California, San Diego (UCSD) Antiviral Research Center (AVRC), under the leadership of Drs. Constance Benson and Richard Garfein, to enroll additional HIV-infected patients from the Owen Clinic of the AVRC UCSD.

Potential numbers of patients with LTBI, by population characteristic, that are eligible to be enrolled in the proposed TBESC study (see Table 1 below)

In each of the three counties, the clinics operated by the TB program will participate in the TBESC studies and provide access to the high risk subsets that represent the target populations for study. In Orange, the participating clinics will be the two Orange County Health Care Agency (OCHCA) Pulmonary Disease Services clinic locations in the cities of Santa Ana and Westminster, the HIV clinic located on the same campus as the TB Clinic in Santa Ana, as well as the Refugee Health Services Clinic in Westminster. In San Diego, the County's Health and Human Service Agency's TB clinic, the Refugee Clinic of the Catholic Charities Diocese of San Diego, and the Owen HIV Clinic at the University of California San Diego will participate. In San Francisco, the TB clinic located on the San Francisco General Hospital campus will participate. In Orange, the TB clinics together evaluate 7,182 patients for TB each year (2007-2009 average). In San Diego, the TB clinic evaluates 6,000 patients, the refugee clinic 2,000, and the Owen HIV clinic approximately 4,000 patients with TST placement and reading or IGRA each year. In San Francisco, the TB clinic sees approximately 3,250 patients for TB evaluation each year. The total annual number of patients evaluated for TB in the TB clinics in the proposed catchment area is over 22,000.

Details of each site's catchment area and study population are described below (in addition, please see Table 1 below):

San Francisco County Tuberculosis Control Program

The city and county of San Francisco has a diverse population of 805,000 (12), 34% of which is foreign-born. Of foreign-born persons, 62% were born in Asia, 20% in Latin America, and 1% in Africa[12].

In 2007-2009, the San Francisco TB clinic evaluated 3247 patients for TB per year: 2267 (70%) patients had LTBI, 944 (42%) were started on treatment for LTBI, and 657 (70%) completed treatment for LTBI. Of the potential pool of study participants, 2168 (67%) were foreign-born, 165 (8%) were recent arrivers to the U.S, 617 (19%) were homeless, 88 (3%) were HIV-positive, and 46 (1%) were children younger than 5 years old.

The TB clinic plans to enroll subjects at high risk of LTBI from the pool of patients who are referred from community providers, and who are immigrants with B-notifications. In 2009, there were 1532 patients with LTBI from these populations; including 177 (12%) recently-arrived foreign-born individuals, 949 (62%) foreign-born individuals who had lived in the U.S. for more than 2 years (a locally defined population with high risk for LTBI), 342 (22%) homeless individuals, 87 (6%) individuals with diabetes mellitus, 49 (3%) drug users, 32 (2%) HIV-infected individuals, 6 (0.4%) children younger than 5-years old.

In 2009, the San Francisco TB clinic completed evaluation of 232 Class B1/B2 immigrants and 1,748 patients referred by community providers. These patient populations included individuals at high risk for LTBI and TB: 4% of the population evaluated at the San Francisco TB clinic in 2009 had HIV/AIDS, 7% had diabetes mellitus, 17% were foreign-born new arrivers, 58% were

foreign-born from high-risk countries, 29% were homeless, and 1% were children younger than 5 years old. Clinic operations and patient care are directed by the TB controller, Dr. Masae Kawamura.

Orange County Tuberculosis Control Program

Orange County has a diverse population of 3.01 million, of whom 30% are foreign-born. Of the foreign-born residents of Orange County, 50% were born in Latin America, 40% in Asia, and 1% in Africa[12].

The Orange County Health Care Agency (OCHCA) tuberculosis program directly oversees patient care at two clinics located in Santa Ana and Westminster. The Director of these clinics is the TB controller, Dr. Julie Low. Populations served by these clinics include refugees, immigrants with B-notifications, contacts to infectious TB cases, and HIV-infected individuals who were referred for TB evaluation from the county's HIV clinic, located on the same campus as the TB clinic in Santa Ana. The OCHCA TB program evaluates 7182 patients for TB per year (average of 2007–2009 data), 2467 (34%) patients had LTBI, 1464 (59%) were started on treatment for LTBI, and 1082 (74%) completed treatment for LTBI. Of the potential pool of study participants with LTBI, 212 (9%) were children less than 5 years old, 2109 (85%) were foreign-born, 448(18%) were recent arrivers to the U.S, and 62 (2%) were homeless.

OCHCA plans to enroll patients with LTBI from populations of individuals arriving with B-notifications, refugees, contacts to infectious TB cases, and HIV-infected individuals referred from the HIV clinic. In 2009, 2068 patients with LTBI were identified using either TST or QFT-GIT at the OCHCA TB clinic from patients in these groups; 1874 (91%) were foreign-born, of whom 538 (29%) were new arrivers.

OCHCA proposes to recruit patients from the pool of individuals who are evaluated at the Santa Ana and Westminster clinics, including contacts to infectious TB cases, refugees, and Class B1/B2 immigrants, as well as HIV-infected individuals referred from the HIV clinic. During 2007-2009, this patient population included 212 children younger than 5 years old who had LTBI. Of the contacts to infectious TB cases that were evaluated at the OCHCA TB clinics in 2007-2009, 36% were born in the U.S.

In 2010, Orange County reported 224 cases of tuberculosis, the 2nd highest number of TB cases in California, and a rate of 7.0 per 100,000 residents; the 8th highest TB rate in the state. Asian (66%) and Hispanic (26%) persons accounted for 92% of Orange County's total TB cases for 2010. Orange County is home to persons who emigrated from countries with high rates of TB; of 224 TB cases, 90% were among persons born outside the United States: 42% from Vietnam, 20% from Mexico, 10% from the Philippines, 6% from Korea, 5% from India, and 3% from China. By comparison, 61% of U.S. 2010 cases and 78% of CA 2010 cases with known birthplace were foreign-born.

San Diego County Tuberculosis Control Program

The county of San Diego is the second most populous county in California and has a diverse population of 3.10 million, of whom 23% are foreign-born. Of the foreign-born residents in San Diego, 53% were born in Latin America, 34% in Asia, and 2% in Africa. Non-Hispanic whites comprise the majority (50%) of the population, followed by Hispanics (33%), 11% Asian, 6% African American[12]. In addition to a steady arrival of new immigrants each year, San Diego receives more than 3,000 refugees each year.

In 2010, San Diego County reported 222 cases of active TB, with approximately 50% among Hispanics, 33% among Asians/Pacific Islanders, and <10% among both African Americans and non-Hispanic whites. TB cases born outside the United States comprised 72% of the total. Among foreign-born cases, the top three birth countries were Mexico (40%), the Philippines (26%), and Vietnam (8%).

In 2007-2009, the San Diego TB and Refugee Health Services Program evaluated 8000 patients for TB per year. An annual average of 1078 patients were diagnosed with LTBI, 459 (43%) were started on treatment for LTBI, and 310 (68%) completed treatment for LTBI. Of the potential pool of patients, 939 (87%) were foreign-born, and an estimated 676 (63%) were recent arrivers to the U.S. At the Owen HIV clinic at the University of California San Diego (UCSD), an estimated 10% (295/2906 persons with HIV and available TB screening data) had HIV/TB co-infection.

The San Diego TB program proposes to enroll patients with LTBI from populations of immigrants with B-notifications, including children with B2 LTBI notifications, refugees, contacts to infectious TB cases, and, in collaboration with UCSD, HIV-infected persons who attend the Owen clinic. In 2009, the San Diego TB clinic identified approximately 1418 patients with LTBI in these groups (in the HIV clinic, an estimate for the year 2010 was used). Of these, 1140 (96%) were foreign-born. TST was used to identify LTBI in adults with B1 notifications, refugees less than 12 years-old and contacts; and QFT-GIT was used in refugees older than 12 years, and children with B2 LTBI notifications.

The patient populations that will be considered for study participation include: adult immigrants with B1 notifications, immigrant children with B2 LTBI notifications, contacts to sputum smear positive TB cases, refugees, and HIV-infected persons. San Diego County receives approximately 400 adult B1 immigrants per year; 80% of whom are born in the Philippines, and 10% each, of whom were born in the Vietnam and Mexico. Among this group, active TB disease is identified in less than 1%, and 250 are diagnosed with LTBI (140 Class II, and 110 Class IV). Approximately 400 children with B2 LTBI notifications are evaluated annually in the San Diego TB clinic; with approximately half born in Mexico and half born in the Philippines. In 2009, San Diego conducted an evaluation of the utility of QFT-GIT in this population: of 250 QFT-GIT tests in children with B2 LTBI notifications, 81 (32%) were positive. Approximately 500 contacts to sputum smear positive TB cases were investigated in 2009: 40% were identified with LTBI. Among contacts identified with LTBI: more than 50% were Hispanic, 27% Asian, 13% black, and 5% white. Nearly 40% were born in Mexico, 25% in the U.S., and 15% in the Philippines. The San Diego TB and Refugee Health Services Program operates a clinic under the authority of the TB Controller, Dr. Kathleen Moser.

Table 1. High risk populations with LTBI proposed for enrollment at CDPH TBCB site

	2009 n (%)		
	Orange	San Diego	San Francisco
Total # diagnosed w/ LTBI	2068	1418	1768
Immunocompromised	-	-	4
HIV infection	11 (4)**	295 (10)**	32
Diabetes	15 (5)†	16 (5) †	87

Cancer	0 †	2 (0.6) †	9
Chronic renal failure	0 †	0 †	-
Immigrants w/ B class	289	334	141
Refugees	249	578	
Other foreign-born	158	169	987
Contacts	230	211	234
Homeless	52	-	342
Incarcerated	-	-	
Drug using	312	-	49
Pediatric (<5 y)	144	12	6
Children (5-14 y)	392	98	50
Recent arriver (≤2 y)	538	-	316
LTBI diagnostic method	TST, QFT	TST, QFT	TST, QFT
Foreign born w/ LTBI	1874 (91)	1140 (80)	1302 (74)
Started LTBI tx	1267 (61)	576 (41)	799 (45)
LTBI tx regimen	INH6 INH9 R4, R6	INH9	INH6 (90) IR4 (10)
FB with LTBI starting treatment	-	441 (39)	445 (40)
USB with LTBI starting treatment	-	129 (46)	115 (28)
Started LTBI with incentives/eblers	78 (6)	0	0
Completed LTBI tx	1016 (80)	439 (76)	565 (71)
Of those w/ LTBI, progressed to TB dz	11 (0.5)	4 (0.3)‡	1 (0.07)

Notes: " - " indicates that data were not available.
*Source: CDPH Aggregate Report for TB Program Evaluation (ARPE) data of contacts with LTBI
**The Orange County HIV clinic has LTBI data on only 20% of its HIV positive clients. 11/271 (4%) in 2010 (the only year of available data) is shown in this table. In San Diego, 295/2990 (10%) of UCSD Owen HIV clinic clients with data on LTBI (of total n>4,000) had LTBI (estimate is for year 2010, but listed here in the 2009 column).
†Orange and San Diego do not routinely collect information on medical risks or co-morbid conditions about their patients with LTBI. These figures are from the subset of foreign-born arrivers with a B-class at the time of evaluation in 2009, based on Electronic Disease Network (EDN) data. Using the denominator estimates in row 7 (provided by the jurisdiction), the prevalence of diabetes among immigrants with a B-classification is 5% (15/289) in Orange, and 5% (16/334)in San Diego.
‡The percentage calculation shown here is based on the total denominator of 1418 with LTBI (row 1). However, in San Diego, data on progression from LTBI to TB disease were available only for the 295 with HIV co-infection (row 3).

B. Approach for recruitment of subjects

A variety of high risk populations are proposed for recruitment at the CDPH TBCB partner clinics, including foreign-born recent and remote arrivers, high risk U.S. born persons (e.g. homeless, substance users), children younger than 5 years old, HIV-infected persons, and persons with diabetes mellitus. At all CDPH TBCB partner clinics, TB program staff, including registered nurses and other health workers (see Section III "Management of the Project"), will recruit study subjects. Eligible patients will be approached and then referred to a study nurse for enrollment. Each clinic will provide language interpretation services for patients that are recruited for the study according to their standard procedures used for all patients. The Research Nurse Coordinators at each site will ensure that patient consent forms are understood and signed prior to study enrollment. Informed consent will be obtained from all study participants. At each clinic, the clinic nurse (or a person in an equivalent position) will make the initial contact with the patient to briefly explain the study and ask for permission to have the study nurse contact the patient. If permission is given, the clinic nurse will "flag" the patient as a potential study subject in the clinic records, and will inform the study nurse who will contact the patient. The study nurse will explain the study in more detail to the potential study enrollee, explain the informed consent form, and obtain the patient's consent if the person agrees to participate in the study. Study participants will be provided incentives to participate in the study (with disbursement at the time of study enrollment, and another disbursement to be provided at end-of-treatment (or at the time treatment should have been completed) for treatment acceptors and decliners. At the time of enrollment, the Research Nurse Coordinator (or other study staff, see "Management of the Project" section for details) will draw blood for QFT-GIT testing and place a tuberculin skin test (TST), and instruct the study participant to return for a TST reading visit.

C. Capacity to collect on the required forms, manage and analyze the data forms: Pre-enrollment form; study entry form; IGRA/TST form, LTBI form; LTBI treatment follow-up form; LTBI treatment closing form; follow-up form for TB; TB disease form; close-out form; cumulative summary form (monthly)

Data will be collected, at each clinic site, on the pre-enrollment form, study entry form, IGRA/TST form, LTBI form, LTBI treatment follow-up form, LTBI treatment closing form, follow-up form for TB, TB disease form, close-out form for each patient approached and/or enrolled in the study. All data elements described in the SOW and in the study protocol will be collected and entered into the CDC-developed data entry system using a password-protected entry system. All standard procedures, in addition to protocol-specified procedures, will be followed to ensure patient confidentiality and data security. At each clinic the study research team (including the Research Nurse Coordinator and study epidemiologists/research assistants) will be responsible for collecting complete and accurate data on each patient. Patient data forms will be entered into CDC's password-protected data entry system at each clinic site by research assistant/epidemiology staff. The CDPH Project Coordinator will ensure completion, entry and submittal of all forms, including the monthly cumulative summary forms, which she will complete, enter and submit. The Project Coordinator will create a database to track total site enrollment, completion of patient follow-up, and quality assurance steps taken; she will analyze these data to inform next steps in internal quality assurance processes, to monitor and track patient enrollment and follow-up appointments and study tasks, and to communicate progress and next steps with local site co-Investigators and clinic study staff, and to create summary reports to be submitted to the CDC study PI.

CDPH TB Control Branch has demonstrated the ability to collect a variety of patient data, derived from multiple sources, for over 2000 study subjects while a member site of the current

TBESC. The California site has participated in the following TBESC studies: Task Orders #3, #7, #8, #9, #13 (3 phases), #25, #28, #29, #33. For the majority of these studies we contributed the largest study sample and shared with other sites our experience in successful data collection and overcoming key barriers. For the mortality study (TO#25), we contributed a data abstraction tool we had previously developed and piloted, as the basis for data collection for this study. Each of our proposed collaborating TB program sites have contributed study subjects to our TBESC studies, and have at least 10 years' experience in providing access to patient records, facilitating patient recruitment and access to external patient records (e.g. hospital discharge and billing records), and contributing to data collection.

CDPH has extensive experience in studies in which data is collected from multiple sites throughout California and analyzed. Data can be entered directly on-site at the local clinic into the centralized CDC web-based system or can be collected by CDPH Project Coordinator and merged for submission of data through the central CDPH TBESC site. Project coordinators, Katya Salcedo, and before her Sumi Sun, successfully coordinated the collating and management of data from multiple clinic study sites in California for TO#3, TO# 8, TO#9, TO#13, TO# 25, TO#28 and TO#29. For Task #9 which enrolled patients from 4 different jurisdictions, data entry occurred centrally and submission to CDC was initiated centrally by our Project Coordinator. Quality assurance checks and data analysis occurred centrally. Similarly Task 25 collects and collates data from 16 jurisdictions. For all TBESC studies, data collection from each jurisdiction is tracked with a spreadsheet created by the central Project Coordinator. The Project Coordinator receives weekly reports from all data abstractors/interviewers (and, for the proposed study, will receive weekly reports from all site Nurse Research Coordinators) on enrollment, and status of data collection efforts (for the proposed study, these data will be associated with study patient monitoring and follow-up). The spreadsheet is used to track enrollment of study participants, including number of study enrollees with complete information, remaining data to be collected, and the types and number of internal and CDC quality assurance steps that have been taken. The Project Coordinator analyzes the data in the spreadsheet, and uses it to monitor enrollment and data collection progress, to inform next steps for internal quality assurance processes, to prompt additional steps to improve enrollment, if necessary, and to generate summary reports for the CDC study PI.

As detailed below, each TB control program site has extensive experience with data collection for patient management, surveillance, and research purposes. All sites have electronic databases for storing patient information, and for tracking patients (e.g. appointments). TB control staff will collect relevant demographic and clinical information using standard TB clinic forms. Additional information collected for study purposes only will be collected by patient interview and/or chart abstraction by the study team. Research staff at all sites will be responsible for collecting, managing and assuring the quality of data collected on the required forms. Responsibility for analyzing study data will be with CDPH staff. Research staff will have access to all primary source data that are collected during routine patient evaluation and care activities at the clinic, if these data are from patients who provided informed consent and are necessary for the study. These data include patient demographic, clinical, treatment, and outcome information.

San Francisco County Tuberculosis Control Program

The San Francisco TB clinic has extensive experience in data collection for public health surveillance, program evaluation, patient management, and research purposes. Additionally, the clinic in San Francisco has extensive experience participating in the TBESC and the TBTC. San Francisco enrolled 57 patients in TBESC TO#9 and 346 patients in TBTC Study #26 (see

Appendix A). The clinic maintains a database that stores demographic, clinical and treatment data that are routinely collected on each patient. The addition of research staff will allow collection of study data on study forms, in addition to currently collected data at the clinic.

Orange County Tuberculosis Control Program

The Orange County Health Care Agency (OCHCA) TB program has extensive experience in data collection for public health surveillance and program evaluation purposes, and has participated in all data collection activities for the current TBESC; the OCHCA TB clinic enrolled 8, 98, 92, and 8 study participants in Task Orders 8, 9, 25 and 28, respectively. The TB program has recent additional research experience which involved enrolling and collecting data from 250 patients with LTBI from refugees and immigrants with B-waivers, "The role of antibody proteomic arrays in the diagnosis and therapeutic monitoring during TLTBI and active TB disease" (see Appendix A). The clinic maintains a database that stores demographic, clinical and treatment data that are routinely collected on each patient with active TB disease, and for tracking contacts to infectious TB cases. The addition of research staff will allow collection of study data on study forms, in addition to currently collected data at the clinic.

San Diego County Tuberculosis Control Program

The County of San Diego TB Control -TB Clinic has extensive experience in completing required forms for research, surveillance, and patient care purposes. The San Diego clinic participated in the TBESC and TBTC. The San Diego clinic enrolled 65, 97, and 9 subjects for TBESC studies 9, 25, and 28, respectively, and 225 patients for TBTC study 26 (see Appendix A). The clinic maintains a database that stores demographic, clinical, and treatment data that are routinely collected on patients with active TB disease. There is also a registration system for all patients, regardless of TB or LTBI status, that includes service and patient information (e.g. demographics), used for making appointments and billing, as well as an electronic database to follow clients with B-notifications, and a paper-based system to collect demographic, clinical and treatment data on contacts to infectious TB patients. The addition of research staff will allow collection of study data on study forms, in addition to currently collected data at the clinic.

D. Capacity to adequately provide LTBI preventive therapy and to follow LTBI patients (both those accepting and refusing preventive therapy) for a total of two years

The three TB programs and their respective clinics have extensive experience in longitudinal follow-up of TB case patients and patients with LTBI to determine progression to TB disease. Routine clinical practices by these three programs in California follow recommendations in published state and national TB treatment guidelines (American Thoracic Society guidelines on LTBI, MDR survival guide, CDPH/California TB Controllers Association Joint Guidelines on B-notification, TB treatment, and LTBI treatment). These guidelines stipulate extended follow-up for several groups at high risk for TB disease with treated or untreated active TB and LTBI. Patients with multidrug-resistant tuberculosis (MDR TB) are routinely followed for 18-24 months during treatment and an additional 2 years post-treatment. Similarly patients who are contacts to MDR TB with an LTBI diagnosis who do not receive treatment for LTBI are followed for 2 years with visits every 6 months that include symptom review, and chest radiograph. MDR TB contacts that are treated for LTBI, are monitored with symptom review at 6 months and 1 year post-treatment. Patients who arrive following TB treatment overseas who are culture negative or not retreated are also followed for 1 year post-arrival with regular monitoring visits. In San Francisco, all patients treated for active disease are followed for one year post TB treatment with monitoring visits. Retention of patients during follow-up has been high in each program.

Methods for follow-up by each program include use of incentives, food, housing, linguistic and culturally matched case managers, social workers, educational interventions, accessible clinic hours and home visits. A combination of phone calls, letters, home visits and automated reminders has helped retain patients. These methods, in addition to study-specific incentives and processes, will be applied to encourage study participation of patients during the two-year follow-up period.

Under study conditions, each program has successfully followed several study cohorts for an extended period to determine progression to TB disease. Both San Francisco and San Diego programs participated in several CDC sponsored clinical trials, including TBTC study 26. Patient retention in these studies was high. All three programs have used monetary incentives, gift cards, travel (e.g. bus passes), food vouchers to compensate for time and inconvenience of patients enrolled in studies. Home visits comprise an important part of case management and contact investigation. Public health nurse and outreach worker home visits also ensure patient retention in studies, provide an ongoing relationship and continuity of care which fosters optimal participation in research studies. Incorporating research activities in home visits also increases convenience for patients, Patients can ask questions and better understand the relevance of their treatment and of a given study protocol. Many of the TB control clinic and outreach staff are bilingual and/or bicultural. These strategies promote optimal patient retention in studies. Supporting the ability to retain special populations with LTBI, San Diego was funded by CDC to evaluate LTBI testing and treatment in high school students and community centers. San Diego enrolled 273 patients with 78% of those completing therapy. For the TBESC study on Latent TB infection (Task Order #13) CDPH TB Control Branch team recruited and followed 170 patients, 89 of whom were treatment decliners, and successfully followed this cohort for one year. The research assistant followed the study protocol and procedures for monitoring and periodic patient interviews.

Providing LTBI treatment and monitoring patients on LTBI treatment is a routine function of the clinics at all three sites. Each site has systems in place for educating patients regarding LTBI, LTBI treatment, and LTBI treatment side effects. Each site also has a system for tracking patients on treatment and monitoring for the development of side effects. Additionally, these sites have systems to encourage treatment completion that include phone calls for missed visits, incentives and enablers when appropriate, and DOPT for certain groups of patients. Following patients longitudinally is also routinely done by these programs for patients with active TB; those systems will be adapted and applied by study staff to follow enrolled study participants with LTBI every 6 months for 2 years regardless of treatment status to assess signs and symptoms of tuberculosis, and to record findings. Additionally, the study nurse will collect blood at the end of treatment for patients who started treatment for LTBI, and at the time that treatment should have been completed for enrolled patients who declined treatment. TB clinic staff will be used as translators when necessary. Additional study staff will be hired to assist the study nurse in patient enrollment, patient tracking and follow-up, data collection, quality control, data entry, and study coordination, communication and quality assurance tasks.

As evidenced by the data below, all three sites are very experienced and successful at adequately providing and following LTBI treatment.

San Francisco County TB Control Program

According to 2009 data, at the San Francisco TB Control Program, 799 patients were started on treatment for LTBI, and 565 (70%) completed treatment for LTBI.

Orange County Tuberculosis Control Program
According to 2009 data, at the Orange County TB Control Program, 1267 patients were started on treatment for LTBI, and 1016 (80%) completed treatment for LTBI.

San Diego County Tuberculosis Control Program
According to 2009 data, at the San Diego County TB Control Program, 576 patients were started on treatment for LTBI, and 439 (76%) completed treatment for LTBI.

E. The methods that will be used to treat and follow LTBI patients (both those accepting and refusing preventive therapy) for two years. This should include how LTBI preventive therapy will be provided (clinic-administered, self-administered, etc.), whether any incentives will be offered, and the mechanisms that will be used to notify or contact the LTBI patient for two years. Any data documenting successful use of innovative approaches to administration or completion of LTBI preventive therapy should be included.

At each clinic existing systems, as well as study-specific methods, will be used to treat and follow LTBI patients. The majority of patients with LTBI who accept treatment will be provided self-administered therapy (SAT). All study patients will be treated according to national treatment guidelines and/or study protocol. The details of the systems and practices of each site are presented below including innovative practices used at those sites. At all three sites, clinical and research staff will extensively educate patients regarding LTBI, LTBI treatment, and LTBI treatment side effects. Each site will use CDC recommended regimens for LTBI treatment. The Research Nurse Coordinator and additional study staff will follow enrolled study participants with LTBI every 6 months for 2 years regardless of treatment status to assess signs and symptoms of tuberculosis, and to record findings. Patients will be notified of follow-up appointments with phone calls and letters by linguistic and culturally matched case managers and study staff (see details below). The 6-month follow-up appointments will be implemented either as in-person clinic visits or phone calls. Additionally, study staff will collect blood for QFT-GIT tests at the end of treatment for patients who started treatment for LTBI, and at the time that treatment should have been completed for enrolled patients who declined treatment. TB clinic staff will be used as translators when necessary. Additional study staff will be hired to assist the study nurse in patient enrollment, patient tracking and follow-up, data collection, quality control, data entry, and study coordination, communication and quality assurance tasks. Incentives will be provided to study enrollees at the time of study enrollment, and at the time of the follow-up venipuncture for QFT-GIT testing (i.e. at the time of treatment completion for treatment acceptors and the time that treatment would have been completed for treatment decliners).

San Francisco County Tuberculosis Control Program
The majority of LTBI patients will be treated by self-administered therapy (SAT) and come to the TB clinic for monthly follow-up and refill appointments. During the initial visit, the clinic physician, registered nurse and health worker will provide education and provide the patient with an informational brochure on LTBI (in the appropriate language). All patients, including those refusing treatment, will be requested to provide current contact information as well as information for emergency contacts. This information will be stored in a data system for quick retrieval, when necessary. Each patient will be assigned a health care worker (who speaks the patient's primary language) who will contact the patient when appointments are missed or follow-up is needed. A patient management database that includes demographic, clinical, treatment, outcome, and appointment data for all patients seen at the clinic will be used to track missed appointments. Clinic and study staff can use the database to print line-lists of patients

who are due for follow-up appointments and/or phone calls. Appointment rescheduling and notification letters will be printed directly from the clinic's patient management database. The current follow-up protocol for missed appointments will be used to monitor and ensure complete participation by study subjects. This protocol includes a phone call and letter to notify the patient of the missed appointment at least four times (once per week for 3 weeks, and at least one more time). TB clinic staff also have access to several citywide databases, including the community clinic electronic record, homeless shelter reservation system and jail health system to find patients who have missed appointments. These citywide databases will be used for the study, if necessary.

Homeless and drug-using patients (and some other patients at very high-risk of TB disease and/or transmission if breakdown occurs) are currently, and will be, for study purposes, treated using directly observed preventive therapy (DOPT). These patients are given medication twice per week and are provided food vouchers and bus tokens as incentives/enablers. Many of these patients are treated in partnership with a nearby outpatient opiate treatment program to help ensure compliance and completion of therapy. If resources allow, San Francisco will implement an automated appointment reminder system which has worked well in the past.

Orange County Tuberculosis Control Program

TB clinic staff in the County of Orange Health Care Agency provides extensive education, (written and verbal, in language appropriate for the patient whenever possible), on LTBI and TB disease. LTBI medication, laboratory tests, chest radiographs, and follow-up clinical monitoring is provided without charge to the patient. SAT is the usual treatment administration method although DOPT is provided, and may be provided under study conditions, to children under 5 years old who are known contacts to infectious TB cases and selected LTBI cases (HIV positive persons, persons with mental illness, substance abusing patients). The program uses incentives/enablers such as gift cards, grocery cards, gas cards, and bus passes to encourage completion of LTBI treatment. These incentives have been used successfully to ensure patient follow-up and treatment completion as demonstrated by the high percentage of LTBI patients who complete treatment (80%). The TB Clinic has a protocol for locating LTBI patients who miss appointments or are lost to follow-up. A study recently conducted on the role of proteomics in LTBI diagnosis followed patients for over a year in the Orange TB clinic.

San Diego County Tuberculosis Control Program

Most patients with LTBI will be treated with SAT. However, some patients may be provided DOPT. San Diego TB control program has been using an innovative strategy of DOPT by video for more than 8 years. It has been a valuable tool to improve surge capacity for DOT. Patients have reported satisfaction with this approach, and the program had documented savings due to time in travel and mileage. In addition, Drs. Garfein and Moser are currently collaborating on an NIH-funded pilot study to develop and evaluate the feasibility and acceptability of conducting video-DOT for active TB using smartphones. For an LTBI treatment program using this technology and approach is a good alternative to in-person DOPT, particularly in a County with 4200 square miles.

Monetary incentives, travel and food vouchers are used to compensate for time and inconvenience of patients enrolled in studies. Home visits comprise an important part of case management and contact investigation. Public Health nurse and outreach worker home visits also ensure patient retention in studies, provide an ongoing relationship and continuity of care which fosters optimal participation in research studies. Incorporating research activities into these home visits also increases convenience for patients. Patients can ask questions and

better understand the relevance of their treatment and of a given study protocol. Many of the TB Control Clinic and outreach staff are bilingual and/or bicultural. In addition, TB Control has well-established links with community-based organizations (CBO) which serve populations (e.g. refuges, homeless) at risk for LTBI and active TB. The San Diego investigators take advantage of their staff's special skills and enlist the support CBO personnel to assist with recruitment and retention. These strategies are used to promote optimal patient retention in studies. Supporting the ability to retain special populations with LTBI in research projects, San Diego enrolled 273 in a CDC funded targeted testing project with 78% of those with full outcomes known completing therapy.

Specific innovative strategies for ensuring completion of LTBI therapy have included video DOT program. Video DOT has been used for treatment of TB cases for over 8 years. Patients have reported satisfaction with this approach and the program has documented savings in travel time and mileage. This program- also part of an NIH-funded pilot study in collaboration with Dr. Garfein at UCSD- uses video-enabled cellular phones to conduct remote directly observed therapy for treatment of active TB. Patients agreeing to the Video DOT program use a smartphone to record and send a video of them taking each of their medication doses. Once the video is sent, a TB program manager views the videos to assure the dose was taken. Patients also receive reminders and confirmation texts on their smartphone. Patients who fail to send their videos within a preset time window are immediately contacted to assure a dose is not missed. This intervention is intended to significantly decrease the costs and improve patients' compliance with TB treatment and also allow staff to focus resources on patients who don't take their medicines. This method could be considered in the future TBESC studies that test new approaches to adherence particularly for regimens such as the 12 week INH/rifapentine DOT regimen. A second innovative and successful strategy has been the Treasure Chest program, a behavioral intervention that employed the behavior modification, techniques of self-monitoring and the use of positive reinforcement (incentives) to increase adherence to LTBI treatment in children aged 14 and under. At their initial clinic visit, each child was provided with a monthly calendar and 30 stickers. The child was instructed to place a sticker on the calendar each day medication was taken, and to bring the completed calendar to their next appointment. When the completed calendar was returned to program staff, the child was allowed to select a stuffed animal or toy from the Treasure Chest as a reward for taking the medicine. The child was then given the next month's calendar and a month's supply of stickers. This procedure was followed at each monthly clinic visit until the child completed therapy, and was determined to increase completion of therapy[13]. This method will be used to improve retention of study participants who are children.

The Owen Clinic

HIV- positive patients are seen semiannually at the Owen Clinic for routine care with interim visits as needed. Patients are reminded of upcoming visits via phone calls and other modes of communication approved by the patient. For patients enrolled in research protocols, information is placed in their clinic charts to notify clinic staff if the patients are due for a study procedure at the time of presentation. This system has been effective for study retention. Study staff also builds rapport with participants to gain their trust and garner support for research. Retention rates of > 80% over 1-2 years of follow-up have been obtained among a difficult to retain population- injection drug users

F. Capacity to monitor LTBI patients on preventive therapy for TB disease and complications of LTBI preventive therapy

Each clinic is fully staffed with physicians for treatment and examination and nurses and outreach workers for observation and follow-up. The TB controller or staff physician is available for consultation at each clinic daily. Each TB controller will be fully oriented to the study as a trained co-investigator and will be responsible for initial response any adverse medical events during studies comparing treatment. During and after treatment, monthly nurse visits will occur, with 6 month symptom and sign review. Each study subject will be followed by the assigned study nurse and the assigned ancillary study personnel. Visit compliance will be monitored with a tiered approach to minimize follow-up loss. The approach will include phone calls, letters, home visits, and incentives and clinic visits at a time convenient for each patient. The relationship built with the study nurse will motivate adherence as well. Tracking to assure appointments and follow-up communications of each study patient will occur through efforts of the study nurse and study research assistant /outreach worker. Patient education is integrated into the initial visit and subsequent monitoring visits at each clinic. During the initial visit , patients are educated on how to take the medication, possible side effects, and are given a return appointment date for medication refill, dispensed from the TB clinic. At the second and all subsequent appointments, the patient is assessed for side effects. The patient is told to call or return to TB clinic if side effects or TB-like symptoms develop. A physician is available daily for evaluation at each clinic of patients with complaints of any adverse reaction or TB symptom. For serious reactions, patients have emergency phone contact and referrals to the nearest emergency room. The documentation and approach to both TB and adverse events will follow the finalized study protocol and procedures. For study enrollment, the PI is listed on the consent form and is available for any question and notified of any serious event.

All three sites currently routinely monitor patients on LTBI treatment at least monthly while on LTBI treatment to assess for development of medication side effects or signs and symptoms of active TB. During the initial visit, patients are educated on how to take the medication, possible side effects and are encouraged to call or return to the TB clinic if side effects or TB symptoms develop. Baseline liver function tests (LFTs) are drawn for patients with risk for hepatitis (i.e. active alcohol use, viral hepatitis, HIV infection, known liver disease). Monthly visits corresponding with medication refills if the patient is being treated by SAT are done, including assessment for TB disease and development of any complications of LTBI treatment. Patients are reminded to immediately contact the TB clinic nurse if side effects are experienced at home. Periodic LFTs are collected per CDC guidelines and at provider discretion or if hepatitis develops during treatment. These patient education and monitoring practices are already routine at all three clinics, demonstrating the capacity of these sites to successfully monitor study participants as well.

San Francisco County TB Control Program

During the initial visit, patients are educated on how to take medication, possible side effects and give a return appointment date for a medication refill dispensed from the TB clinic. At the second and all subsequent appointments, the patient is assessed for side effects. Baseline LFTs are drawn for patients with elevated hepatitis risk and patients placed on rifampin plus INH. Periodic LFTs are collected at provider discretion or if hepatitis develops during treatment. The patient is told to call or return to clinic if side effects or TB-like symptoms develop.

Orange County TB Control Program

LTBI patients are monitored monthly at a minimum in the clinic by registered nurses working under a standardized procedure or in select cases by the TB clinic physician. At each monthly visit, patients are assessed for TB disease and adverse effects by symptom review. Appropriate laboratory tests are drawn as per CDC/American Thoracic Society (ATS) and CDPH/California

TB Controllers Association (CTCA) LTBI treatment guidelines. Under study conditions, the clinical protocol for monitoring will be followed for enrolled patients.

San Diego County TB Control Program

LTBI treatment patients are monitored at their monthly refill visit with a clinic nurse. They are interviewed at this time regarding possible medication side effects. In addition, education is conducted to ensure that the patient will immediately contact the TB clinic/refill nurse if side effects are experienced at home. The new national case report form collects information on risk factors for TB including incomplete LTBI treatment and whether patient was a contact in two years preceding TB diagnosis and whether the patient had a b-notification. This requires tracking data and matching patients in a database over time to identify TB disease development, which the San Diego program routinely performs.

G. Primary source data capacity and ability to collect all the data on the required forms.

Research staff at each site and at CDPH will have access to primary source data for enrolled study participants. Data will be collected by research staff from clinical records and from patient interview for completion of all required forms. As detailed in section C, all sites have experience and capacity for successful data management and collection.

The primary source public health records will be accessed by study personnel that are integrated as part of the public health teams located at each clinic site. Each clinic will have a Research Nurse Coordinator who will be charged with recruitment and accessing records. The clinic clerical and nursing staff will support and facilitate timely patient record access. The CDPH Project Coordinator will also be given access to the primary records with assistance from the research and clinic staff at each clinic site. The CDPH Project Coordinator will arrange for CDC site visits through coordination with the study team located at each clinic. Charts of study subjects with primary clinical and laboratory data will be made available along with their accompanying abstraction forms, at each clinic for primary record review during each CDC site visit.

CDPH has extensive experience in studies in which data is collected from multiple sites throughout California. Data can be entered directly on-site at the local clinic into the centralized CDC web-based system or can be collected by CDPH project coordinator and merged for submission of data through the central CDPH TBESC site. Study coordinators, Katya Salcedo, and before her Sumi Sun, successfully coordinated the collating and management of data from multiple clinic study sites in California for TO#3, #13, TO# 8, TO#9, TO#13, TO# 25, and TO#29. For Task #9 which enrolled patients from 4 different jurisdictions, data entry occurred centrally and submission to CDC was initiated centrally by our study coordinator. Quality assurance checks and data analysis occurred centrally. Similarly Task 25 collects and collates data from 16 jurisdictions. Merging data and matching to the state case registry, and analysis is a routine function for our state epidemiologists which manage a large cases registry and perform matches with multiple databases on a regular basis.

Successful primary record review has been accomplished without difficulty during CDC site visits by project officers for TBESC studies. For example, for Task Order (TO) #13, the Latent TB study, CDPH facilitated access to patient data and CDC personnel traveled to the clinic study site in San Joaquin County and readily reviewed the source data for each abstracted record for quality assurance checks. The public health clinics routinely access hospital and laboratory data for clinical care. They each have established relationship with the hospital

records department and infection control nurse at each hospital. It is through these established relationships that current TBESC study personnel have accessed hospital records, laboratory records, and hospital cost data. When there is little relationship with a small hospital where records are needed or with a hospital cost center, study team has worked with the TB controller, program manager, and infection control nurse to successfully access these records and secure any needed Institutional Review Board (IRB) approvals. To date for the Mortality study (Task Order #25) hospital records have been accessed and reviewed for more than 500 patients. The admission and discharge summary and associated face sheet with discharge diagnoses is frequently obtained by local health department and part of records. Inpatient billing information has been successfully captured for patients with assistance from the hospital infection control nurse.

H. Approach for quality control of TST, IGRA, patient recruitment, data collection and laboratory data

Quarterly quality assurance data checks will be performed to ensure data completeness, use of valid variables and responses, and logical consistency. The Project Coordinator will be responsible for performing quarterly quality assurance. At each site, the Research Nurse Coordinator will supervise the research assistant who performs data collection, data entry, and tracks patients, patient-care activities, study activities, and follow-up activities as specified on the study protocol. Research Nurse Coordinators will perform monthly quality assurance checks, and will work with site research assistants to resolve data discrepancies. If additional assistance is required to resolve data quality/completeness issues, the Research Nurse Coordinators will inform the Project Coordinator and enlist his/her assistance. Additionally, the Project Coordinator will maintain a database to track enrollment, study patient follow-up, and data collection activities (including laboratory, QFT-GIT and TST results) at the clinic sites. The Project Coordinator will analyze these data on a bi-weekly basis to monitor patient enrollment and follow-up progress, and to inform next steps and communication with the site Research Nurse Coordinators to assure timely enrollment and complete data collection.

During the first month of pilot enrollment, the Project Coordinator will visit each clinic site to train the research nurse coordinators and research assistants in study form completion and data entry. During the second month of pilot enrollment, the Project Coordinator will perform quality assurance data checks with each Research Nurse Coordinator to ensure data completeness, use of valid variables and responses, logical consistency, and accurate and complete data entry. At this point, the Research Nurse Coordinator will perform monthly quality assurance checks and the Project Coordinator will review all forms at quarterly intervals. Trouble-shooting and follow-up training may be needed and will be performed by the Project Coordinator if a pattern of incorrect/inadequate data collection is found during the quality assurance checks. In the absence of patterns of incorrect/inadequate data collection, the Project Coordinator will counsel the site Research Nurse Coordinator to correct errors and resolve logical inconsistencies.

Quality and accuracy of TST placement and reading is assured by using only trained staff to administer and read the TST. In San Francisco, both nurses and unlicensed staff place and read the TST; all staff are trained and unlicensed staff have annual refresher trainings. In Orange, only licensed nurses place and read the TST. To assure quality of TST during the study, a trained, experienced nurse, with at least 10 years' experience, will monitor the placement of the TST by the study nurse, and will review the interpretation of the reading of the TST by the study nurse for a random sample of patients.

Data from the laboratories will be generated and transmitted electronically, reducing the risk of data entry errors. Nevertheless, as for all other data collected for the study, data generated by the laboratory will undergo quality assurance and completeness checks by local and CDPH TBCB study staff. Laboratory staff will be contacted to investigate and resolve any discrepancies.

I. A description of how cost data to conduct comparative effectiveness, outcome, and economic analysis will be collected

The CDPH TBCB Project Coordinator will be responsible for /supervise the collection of data for comparative effectiveness, outcome and economic analyses of the study. She will follow study protocols and generate an implementation plan to identify sources of data for: actual costs to the study from host agency, health system components, such as California's TB Medi-Cal system, and third party payers; actual or estimated costs to the patient in the form of lost wages or out-of-pocket expenses for those receiving LTBI treatment. Additionally, demographic, epidemiologic, treatment, medical process, treatment and outcome data will be sought for use in modeling or estimating actual or potential effects of treatment on prevention, e.g. TB cases averted. The study research staff at each site will collect these data on study-generated forms and submit to CDC electronically, using the CDC-developed password-protected data entry system.

CDPH TBCB has demonstrated capacity to conduct data collection and create and interpret models for cost-effectiveness analyses. CDPH TBCB led the development and analysis of four published studies investigating the cost effectiveness of latent TB infection evaluation and treatment[14,15,16,17]. Each of these studies was conceived and implemented by a TBCB senior research scientist under the direction of the CDPH TBCB Principal Investigator. These studies began with a key scientific question, required extensive literature review, complex analysis and modeling, and culminated in publication, with subsequent key program and policy changes. To design and carry out these studies, including model construction, these studies required critical review of the literature on estimates on risk of LTBI to TB progression, risk of drug-related adverse events, including hospitalization, hepatitis and death. The studies also required original collection of data on costs of TB diagnostics and interventions to compute case prevention estimates. The detailed knowledge gained from these studies allows the proposed CDPH TBESC PI to make expert contributions to future studies on LTBI progression and diagnostics and costs proposed as the focus for the new consortium.

J. Recognition of and plans for overcoming barriers that may be encountered during the project

Several barriers may be encountered during this project. The potential barriers include 1) insufficient enrollment due to lower than expected LTBI diagnoses or high refusal rates, and 2) treatment may be accepted or refused at a lower rate than expected and 3) loss during follow-up may be higher than expected. There are many options for expanding patient enrollment if LTBI diagnoses are insufficient for enrollment at a given site. Each site has diverse populations and referral settings for expansion. The advantage of the CDPH TBESC site is the engagement of multiple collaborating clinics. The projected enrollment is a minimal estimate based on 50% or less capture and does not include all potential populations in the target group for approach. If refusals rise above 50%, an assessment of potential reasons for a high refusal rate will occur to determine if factors are modifiable. Similarly, if loss to follow-up exceeds the expected threshold, contributing factors will be examined and interventions to improve retention will occur. The CDPH study team has experience in several TBESC studies with identifying barriers and addressing these successfully to ensure the committed enrollment. For example, in TBESC

LTBI study (Task Order #13), the enrolling clinic in San Joaquin had insufficient LTBI diagnoses. Expansion of enrollment to a second clinic occurred in a timely fashion and study enrollment exceeded the target. Enrollment of MDR TB cases early in treatment proved challenging at the outset of an interview study, Task Order #8, with one of 3 consenting instead of the 50% or more anticipated. In that study, approach was modified to start with the clinic physician rather than the case manager which improved study enrollment rates significantly from below 50 percent to above. Re-education of personnel at each study site regarding the approach script and study purpose also reinforced and contributed to successful enrollment. Effective and timely incentives and reminders tailored to patient populations are an important method for retaining patients during follow-up and will be used in this study. Each enrolling site has extensive experience in following patients with MDR TB for treatment for two years followed by a two year post-treatment follow-up period of monitoring visits. Communication in the primary language of the patient is another critical element of patient retention. All three sites have diverse interpreter staff for approach and consents as needed. The tracking systems assure that prompt action can occur when enrollment falls or a specific subpopulation has lower than expected numbers including treatment acceptors and decliners. The systematic assessment of study barriers by CDPH and collaborator study team includes: 1) reviewing and assessing the approach by study personnel, 2) the methods for reminders, 3) whether incentives are sufficient, 4) the number and types of attempts at patient contact, and 5) the specific choice of personnel conducting each step. Reasons for refusals are examined; ensuring protocol script and measures are followed, consideration of physician/PI approach; and a decision to approach more patients. Prompt notification of the CDC study PI and project officer when a significant barrier occurs is a regular practice by the CDPH site in the current TBESC, and is proposed for this study.

K. A description of the methods used to obtain, process, and interpret the required IGRAs. Include a description of your ability to perform the appropriate and required quality assurance of IGRA, and to monitor and correct any potential problems on IGRA testing

Each clinic will collect blood from patients in the tubes provided by Cellestis for the QFT-GIT: Nil Control tube, TB Antigen tube, and a Mitogen Control tube. Tubes will be labeled with appropriate patient information prior to venipuncture, and will be checked off on a "blood collection spreadsheet." The phlebotomist will shake the tubes after collection according to manufacturer's directions, and place the tubes into a collection bag that is picked up by courier for transport to the public health laboratory for incubation, processing, and testing. Within 16 hr. of collection, the tubes will be incubated at 37 C in the public health laboratory. Following a 16 to 24 hour incubation period in the public health laboratory, the tubes will be centrifuged, the plasma will be removed and the amount of IFN-γ (IU/mL) measured by ELISA. Test results will be interpreted according to manufacturer's instructions and CDC guidelines (5).

As per California State Law, all laboratory testing at the participating public health laboratories is performed by state-certified Public Health Microbiologists. All three public health laboratories have extensive experience performing QFT-GIT and have well-established QA practices in place. See below for detailed descriptions for each laboratory:

<u>The San Francisco Department of Public Health Laboratory (SFDPHL)</u>
The SFDPHL performs QFT-GITS and is a state-of-the-art microbiology laboratory under the jurisdiction of the City and County of San Francisco. The SFDPHL facility encompasses over 4600 square feet of laboratory space, and is equipped with 5 class II biosafety cabinets, 2 robotic DNA/RNA extraction units, EIA testing equipment (for automated and manual

execution), 2 rapid thermocyclers (for PCR), freezers (3x -80°C, 7x -35°C) for the storage of blood and other specimens, and 15 centrifuges for both clinical and molecular operations. The SFDPHL was amongst the first laboratories to test for HIV infection. The lab provides both molecular and conventional testing for a wide variety of viral and bacterial diseases. The laboratory currently maintains two alternative methods for HIV RNA detection (APTIMA COMBO (TMA) and real-time PCR), both to be able to increase capacity further, and to maintain quality assurance by comparison for each technique.

Approximately 120,000 lab tests are performed annually at the SFDPHL, which is staffed by 20 laboratory personnel, 10 of whom are bachelor's-level laboratorians who have been trained and certified by the State of California as Public Health Microbiologists, 1 of whom is a doctorate level scientist. The SFDPHL is fully equipped with over 20 personal computers connected by intranet that are continually staffed by certified network professionals. The SFDPHL has proximity to numerous support facilities, including San Francisco General Hospital, UCSF and UC Berkeley, with whom numerous collaborations take place on a regular basis. The laboratory is funded in part through the City general fund, in addition to a number of federal and state granting sources.

SFDPHL has been performing QFT testing (first generation and subsequent versions) since late 2003 and QFT-GIT testing from 2008 to present. The laboratory and the TB clinic have a long-established relationship. To-date the laboratory has done over 50,000 QFT tests, including approximately 10,000 QFT-IT tests per year. In 2009, the SFDPHL performed 10,329 QFT tests using an automated immunoassay processing device—a DSX Automated ELISA System by Dynex instruments, 2460 smears and cultures for AFB isolation. Between April of 2010 and April of 2011, the lab performed 187 NAA tests for MTB. All QFT testing at SFDPHL is performed by licensed (CA State Certified) Public Health Microbiologists. These staff are evaluated annually for bench level performance, and also perform proficiency testing using panels both internal and provided externally.

The San Francisco Department of Public Health Laboratory maintains quality assurance and quality control protocols on a daily basis towards an effort to maintain the highest level of accuracy and reproducibility in lab testing. In furtherance of this, the laboratory is routinely inspected by the State of California, Department of Health Services with regard to CLIA (Clinical Laboratories Improvement Amendments), by way of Federal mandate. The laboratory participates in quarterly evaluations of the laboratory's ability to perform correctly, specific lab tests. This is done through the College of American Pathologists (CAP) and the American Association of Bioanalysts (AAB). Internally, each section of the laboratory routinely evaluates background specimens, in an effort to ensure that contamination of the laboratory environment is not present. All incubators, freezers and temperature control devices utilized in the laboratory are inspected on a daily basis, with temperatures recorded to ensure consistency of operation. All major equipment is maintained by preventive maintenance and regular service contracts.

Quality assurance for QFT-GITs include: Controls are provided with every batch of QFT specimens analyzed; equipment is maintained through preventive maintenance and service contracts; incubators used for the test are assessed daily for correct performance; microbiologists that perform the test are assessed annually for competency; the laboratory takes part in both an internal and external proficiency testing program (CAP) which involves three annual testing events. All QFT batches are performed with controls whose performance is monitored by senior microbiology staff; oddities and failures are noted with corrective actions taken when necessary.

Orange County Public Health Laboratory
QFT-GIT tests are performed in the Immunology section of the Orange County Public Health Laboratory by certified Public Health Microbiologists. In 2010, 1373 QFT-GIT tests were performed, in addition to 5830 acid fast bacilli smears, 5880 cultures and 547 nucleic acid amplification tests (NAATs), 214 genotyping, and 82 drug sensitivity tests from specimens of patients suspected to have TB. This laboratory is a biosafety level-2 facility that uses a Thermo Wellwash 4MK2 plate washer and a Biotech ELX 800 plate reader to perform QFT-GIT. The laboratory has been performing QFT-GIT testing since April 2009. The laboratory is located across the parking lot from the Santa Ana TB Clinic and 5.73 miles from the Westminster TB Clinic.

Quality assurance is performed at the Orange County Public Health Laboratory through a variety of mechanisms. First, the laboratory is experienced in all aspects of quality assurance of diagnostic tests performed and has the CLIA Quality Assurance Program in place. In addition to general quality assurance standards, QFT-GIT test results are reviewed quarterly as a part of the Patient Test Management review, and the laboratory participates in the external QFT-GIT proficiency testing program (CAP). Additionally, preventive maintenance records are reviewed monthly by the Supervising Public Health Microbiologist. For each QFT-GIT test performed, quality is assured by: running kit quantitative standards in triplicate on each plate in the run; review of all indeterminate results by the Senior Public Health Microbiologist before reporting, and; repeating tests if possible error in test setup was identified. The Senior Public Health Microbiologist corrects and documents problems or errors and notifies the section supervisor.

San Diego County Public Health Laboratory
QFT-GIT tests are performed in the County of San Diego Public Health Lab by State of California certified Public Health Microbiologists. The laboratory implemented QFT-Gold in late 2006, and QFT-GIT in August 2008. QFT-GIT is performed using the Dynex DSX Automated System under BSL-2 conditions. All TB specimen processing and culture work is done in the BSL-3 lab. In 2009 the laboratory performed approximately 3200 QFT-GIT tests and 3800 TB cultures.

The laboratory uses multiple quality assurance/QC mechanisms to perform QFT-GIT tests and for interpretation of results. FDA-approved package inserts are followed for testing, reporting and interpretation. Both the qualitative and quantitative result is reported according to CDC guidelines. The laboratory is enrolled in CAP Proficiency Test Panel QF with two shipments per year. Previously tested positive and negative specimens are included in each run per CLIA guidelines. The laboratory is CLIA-certified. Additionally, QFT-GIT testing is monitored by checking for correct draw volume prior to testing (reported as Unsatisfactory if volume incorrect), incubator temperature is monitored daily and prior to putting in specimens, two microbiologists check QC values including external controls on DSX results worksheet prior to reporting results to make sure that run was valid (results not reported if run is invalid).

III. MANAGEMENT OF THE PROJECT

A. Description of how the work will be organized, staffed, and managed

Organization

The CDPH TB Control Branch is the lead agency in the state of California responsible for TB control. CDPH TB Control Branch provides oversight, funding, and technical assistance for the TB control efforts of 61 local health jurisdictions in California. The California Department of Public Health (CDPH) TB Control Branch proposes to contribute to an effective national research consortium by carrying out studies in collaboration with three local TB control programs in California and their associated clinics. This collaboration will build on the successful scientific collaboration and organization of the current CDPH TBESC site. These programs are San Diego, Orange, and San Francisco Counties.

The CDPH Principal Investigator (PI) Dr. Jennifer Flood, Project Director (Dr. Lisa Pascopella) and Project Coordinator (Katya Salcedo) will function as a central team providing coordination across study personnel located at each participating clinic.

At the three local programs, the TB controllers, who each are nationally recognized TB experts, will be designated as study co-investigators (Masae Kawamura, San Francisco; Julie Low, Orange; Kathy Moser, San Diego). Each of the three local sites will be staffed with a study nurse who will oversee, recruit, and enroll study patients. This research nurse will function as the local site coordinator. Data management and tracking of enrollment and patients during follow-up will be supported by additional research assistant and analyst personnel funded at each local site.

To perform core scientific work, the CDPH TB Control Branch proposes the following organizational structure and roles outlined below (also see Appendix B).

Management

Role of CDPH

The CDPH PI, Project Director and Project Coordinator will function as a central team providing coordination across study personnel located at each participating clinic, and serving as central point of contact for communication with CDC PI and contract officer. CDPH will receive funds from CDC and allocate funds through local assistance awards to each program.

The Principal Investigator, Jennifer Flood, MD, MPH, will oversee the performance of the core requirements. She will participate fully as a member of the Consortium Steering Committee. Dr. Flood will have overall responsibility for ensuring adherence to the policies/procedures, a close collaborative relationship between the CDPH TB Control Branch and our local program collaborators, and ensuring that the CDPH TB Branch and California collaborators abide by the Conflict of Interest Policy. The Project Director, Lisa Pascopella PHD, MPH, will also participate in consortium committees, and will be this contractor's (California's) lead contributor to the development of the Consortium's standard operating procedures and appropriate research protocols. Katya Salcedo, MPH will be the Project Coordinator, responsible for implementing the bylaws, research protocols, and collaborative relationships.

Collaborators will be convened on a regular basis to provide critical input to the PI and Project Director on national protocols. Meetings will occur quarterly and conference calls related to specific studies will occur more frequently. The Project Coordinator at the CDPH TB Control Branch will organize the collaboration and facilitate all communications from CDPH TB Control Branch to local collaborators.

The collaboration will provide a structure to facilitate ongoing communication, orient partners to ground rules and consortium by-laws, provide a method to bring together investigators for discussion of new tasks, report findings of studies and stimulate participation.

The CDPH PI, Project Director and Project Coordinator will also provide an assurance function to monitor milestones for meeting study objectives and ensure reporting is timely and accurate. Progress in research participation and deliverables of all collaborators will be monitored in a systematic fashion by the CDPH TB Control Branch Project Coordinator. Data will be entered per protocol into the centralized national database. Site visits will occur at each clinic and routine checks of enrollment progress, data completeness and accuracy will be conducted by the Project Coordinator.

The PI and Project Director will commit to active participation in each contract requirement including development of standard operating procedures, and research protocols as well as fulfilling consortium commitments of committee participation, analysis, interpretation, and dissemination of study findings. The PI and Project Director, as well as site co-Investigators (two site co-Investigators will travel per year) will travel to the semi-annual national TBESC meetings. The Project Coordinator will help to organize and ensure clear communication to CDC and TBES Consortium, submission of required reports, and develop a monitoring system to assure protocol adherence, reporting, and data and specimen submission is complete by all site participants. The proposed Project Coordinator has over 8 years of experience functioning as a Project Coordinator of complex studies. She has successfully fulfilled this function for our site's participation in the current TBESC and will build on that experience.

Role of Local Program Collaborators

The three local TB control programs will be responsible for participant recruitment, LTBI testing, treatment, monitoring, and follow-up for all study subjects. Each site will be staffed with a study nurse who will oversee, recruit, and enroll study patients. Tracking enrollment and patients during follow-up will be supported by additional funded members of the research team at each site. The Research Nurse Coordinator will function as the site coordinator and each site will have the TB controller designated as a study Co-Investigator. In San Francisco, study staff (a full-time Research Nurse Coordinator and full-time Epidemiologist) will recruit, enroll, and follow patients at the TB program clinics. In Orange, study staff (a full-time Research Nurse Coordinator, half-time Epidemiologist and additional part-time ancillary staff) will recruit, enroll and follow patients at the two TB clinics, the Refugee clinic, and the HIV clinic. In San Diego, study staff (a half-time Research Nurse Coordinator, a half-time Epidemiologist, and part-time phlebotomist/Research Assistant) will recruit, enroll and follow patients at the TB and Refugee Clinics, and the UCSD Owen Clinic. The San Diego site will include study staff employed by University of California, San Diego Antiviral Research Center (AVRC), under the direction of Drs. Constance Benson and Richard Garfein. These staff will recruit patients at the TB program clinics (i.e. the TB clinic and Refugee clinics) and the Owen Clinic of the AVRC UCSD.

Staffing and staff roles

The CDPH PI (Jennifer Flood) will devote 0.10 FTE (4 hours weekly) in-kind and will:

- Serve as main contact between CDC PI and site
- Ensure all research team members understand and fulfill respective roles and responsibilities
- Make sure by direct involvement or supervising work of research team members that study is conducted in accordance with protocol and human research guidelines protecting human research participants

CDPH Project Director (Lisa Pascopella) will devote 0.15 FTE (6 hours weekly) and will:

- Plan and chair study related meetings at site
- Facilitate exchange across CDPH site network
- Identify training needs
- Assure internal QA and ensure accurate data
- Report annually to local IRB on progress and to CDC site progress in enrollment
- Serve on TBESC committees
- Problem solve operational challenges

CDPH Project Coordinator (Katya Salcedo) will devote 0.60 FTE (24 hours weekly) and will:

- Obtain CDPH and local IRB approval for study protocol including amendments, renewals and CDC IRB deferrals
- Draft and maintain all study-related communications with state and local IRBs
- Serve as liaison between the local site research team and local IRB
- Ensure compliance with HIPPA regulations
- Ensure confidentiality maintained throughout study in accordance with study protocols
- Disseminate standardized tracking form per research protocol
- Arrange for and ensure all study team members participate in protocol required trainings
- Develop and implement of QC/QA activities
- Monitor study implementation to ensure study is conducted in accordance with protocol requirements and regulatory guidelines
- Ensure study related meetings and conferences are documented
- Report breaches of confidentiality to CDPH PI

TB Clinic Co-Principal Investigators (Masae Kawamura, San Francisco, will devote 0.10 FTE (4 hours weekly) in-kind; Julie Low, Orange will devote 0.10FTE (4 hours weekly) in-kind; Kathy Moser, San Diego, will devote 0.05 FTE (2 hours weekly), and will:

- Supervise on-site study personnel assigned to clinics
- Contribute to study protocol development
- Assess enrollment capacity
- Assist with hiring
- Contribute feasibility assessment with new studies
- Relate to CDPH Project Director and Project Coordinator

Research Nurse Coordinator will devote 0.50-1.0 FTE (20 to 40 hours weekly) and will:

- Obtain participant incentives and oversee handling and record-keeping of disbursement of participant incentives
- Identify potential participants in coordination with clinic staff and confirm eligibility
- Recruit study participants, in coordination with clinic staff

- Track study participants using Study Participant Tracking Form
- Maintain log of all participants
- Conduct informed consent process with potential participants
- Interview study participants and arrange for interpreters as needed
- Coordinate schedules and logistical requirements of field staff
- Coordinate and assist with supervision of field data collection activities
- Assist with implementation of QA /QC procedures
- Coordinate and oversee data entry activities
- Ensure completion of forms
- Ensure data entry discrepancies are resolved according to approved edit procedures
- Serve as main contact with CDPH project coordinator
- Maintain regular communication with clinic staff
- Ensure study related documentation requirements are being met and study related documents and communications are maintained and stored in a secure and confidential manner
- Participate in staff meetings as requested

Local TB Clinic Study team
Each site research team will be comprised of personnel capable of data entry, interviews, outreach, tracking, phlebotomy and assist with quality control activities.
These personnel will include an Epidemiologist I (San Francisco), a Senior Epidemiologist (Orange) a Research Assistant (San Diego) and an Information Processing Specialist (Orange). Together the local clinic study team will have the capacity to perform data management and data entry, transport specimens to the laboratory, make home visits, assist in tracking with letters, telephone calls and home visits. They will work closely with and support the TB Clinic Study Nurse / coordinator.

Public Health Laboratory Director (Mark Pandori, San Francisco; Richard Alexander, Orange; Patricia McVay, San Diego)

- Oversee performance of study laboratory testing including IGRA testing
- Ensure appropriate and ongoing QA
- Oversee serum specimen storage, handling, and shipping quarterly
- Coordinate and supervise laboratory data collection
- Address any identified problems arising from laboratory testing

The personnel participating in the study include the following (see Appendix C for biosketches):

Members: CDPH TB Control Branch, Local TB Program Partners, and Laboratories

(See biosketches in Appendix C)
The participation of the California TBESC site will contribute a highly experienced team of physician scientists as principal and co-investigators, who have each identified and managed thousands of high risk patients with latent TB infection and led or contributed to multiple complex TB studies. Epidemiologists staffing this consortium site bring a longstanding record of leading and coordinating research and have played a key role in the success of the current TBESC. Public Health Laboratory Directors who are leaders in the field of pathogen diagnostics will partner with each participating local TB program. Finally, experienced program staff including physicians, nurses, epidemiologists, outreach workers and program managers, of high functioning, high morbidity TB programs will support the research team.

For the proposed TBESC, Dr. Jennifer Flood will serve as Principal Investigator, Dr. Lisa Pascopella as Project Director, and Katya Salcedo as Project Coordinator. Dr. Masae Kawamura, Dr. Kathleen Moser and Dr. Julie Low, heading San Francisco, San Diego and Orange TB programs, respectively, will serve as co-investigators. The associated Public Health Laboratory Directors will partner with each program to contribute scientific expertise in evaluating TB diagnostics and ensuring high quality laboratory services needed for each study including the performance of IGRAs.

Jennifer Flood MD, MPH, Principal Investigator, Chief of the California Tuberculosis Control Branch, will function as PI for this site and devote 0.10 FTE in-kind to this effort. She is an Assistant Clinical Professor of Medicine in the Division of Infectious Diseases at UCSF and serves as Attending Physician on the Infectious Diseases Inpatient Consult Service at the San Francisco General Hospital. She has provided clinical care for patients with active TB and LTBI at the San Francisco Department of Public Health TB Clinic for over a decade. She is Board Certified in Infectious Diseases and Internal Medicine. Dr. Flood served as PI for the California TBESC site for the past decade. Under her oversight, the California site consistently met contract requirements for each study funded and actively participated in study and consortium activities. She has extensively published in TB. She also brings experience in evidence-based TB guideline development; she chaired the development of state guidelines on LTBI and TB diagnosis and treatment (1) and Evaluation and Treatment of Persons with B-notification(2), and recently served as an invited consultant on an advisory committee to CDC on recommendations for implementing the rifapentine INH 12 week LTBI treatment regimen. She serves as clinical faculty at the Curry International TB Center and provides training to new clinicians on both latent and active TB disease diagnosis and treatment. She regularly provides consultation to clinicians throughout the state on complex questions related to LTBI and TB diagnosis and treatment. She has served as member of CDC's Advisory Council for Elimination of TB and as a consultant to CDC in evaluation of Immigrant and Refugee TB and LTBI detection and treatment programs in Vietnam and Nepal. As the State TB controller she is responsible for a program that directs efforts to prevent and control the nearly 2500 annual incident TB cases. In California there are an estimated 3 million individuals with latent infection who may benefit from detection and treatment to prevent future TB cases. Since 1998, at the San Francisco TB Clinic, she has managed nearly 3,000 patients with TB infection. This setting serves large immigrant and HIV co-infected patient populations. She will bring this real world experience of identifying and treating a diverse patient population with latent TB infection (LTBI) and active TB disease to research development and analysis of the TBESC.

Dr. Lisa Pascopella, Senior Epidemiologist for the Surveillance and Epidemiology Section, CDPH has extensive research experience and has served on the current TBESC Research Committee since 2006. Dr. Lisa Pascopella will function as project director and devote 0.15 FTE (6 hours weekly) to this effort. Dr. Pascopella received her doctoral degree in microbiology and immunology at Albert Einstein College of Medicine, her post-doctoral training at the National Institutes of Allergy and Infectious Diseases Laboratory, Rocky Mountain Laboratories, and her MPH degree at the School of Public Health at UC Berkeley. Her previous experience in the molecular biology and genetics of *Mycobacterium tuberculosis* is documented by her publications in these areas. Dr. Pascopella's recent work has included epidemiologic studies in recurrent TB in California that include the examination of genetic, clinical and programmatic factors. She has served as faculty for epidemiology courses at the Curry International TB Center since 2005. Dr. Pascopella published a study on laboratory and operational aspects of TB diagnosis that is relevant to the research questions posed by the proposed TBESC. In

addition to providing direction, project management, and intellectual contribution to study design, analysis and interpretation, she will contribute laboratory knowledge and help coordinate the quality assurance aspects of the laboratory component of the study.

Dr. Pascopella has functioned as: Project Director at the California TBESC site for three years, supervising the work of the Project Coordinator and Epidemiologist; and Research Administrator of TBESC studies conducted at the Curry International Center, University of California, San Francisco from 2005-2008. While at the Curry International Center, she directed the multi-faceted Task Order 6 which created and evaluated regional models of collaboration for TB programmatic, epidemiologic and clinical consultation among four low-incidence states. She also directed the close-out of Task Order 9, the epidemiology of TB among the foreign-born in the U.S., and the initiation of Task Order 19, the assessment of treatment completion among persons with LTBI diagnosed with QuantiFERON. She co-chaired the TBESC Translating Research into Practice committee 2007-2008, and has been an active member of the TBESC Research Committee since 2006. She is a co-Principal Investigator for Task Order #29 which examines the identification and treatment of latent TB infection among HIV-infected. For this task she forged collaboration with the Los Angeles Clinics and office of AIDS and LA TB program and successfully implemented this study. The CA site has met all relevant timelines and deliverables to date and has abstracted records of over 300 patients. Dr. Pascopella also directed a 5 year CDC project on Contact Investigation with the objective of tracking contacts with latent TB infection through treatment. She directed the development of a contact investigation database, quality assurance mechanism, a system for tracking patients over time and systematically recording lab results and risk for LTBI progression to disease.

Katya Salcedo, Project Coordinator for the current TBESC California site, is an epidemiologist with over 8 years' experience coordinating and managing operations for the CDPH TBESC research site. She will devote 0.60 FTE (24 hours weekly) to this project. Ms. Salcedo received an award from CDC in 2006 for the Outstanding Project Coordinator. She has extensive experience in developing, interacting and maintaining key stakeholder relationships. She received her MPH at USC in Epidemiology and Biostatistics and BS in Microbiology and Molecular Genetics. She has successfully coordinated complex studies involving many California jurisdictions. She has direct experience in every aspect of study implementation. She has approached and enrolled patients, translated patient consent forms for IRB approval, submitted and gained approval for over 40 IRBs which required forging successful professional relationships with multiple agencies and individuals. She has constructed budgets for multiple studies, tracked study enrollment, performed and directed quality assurance activities, created implementation plans, presented study aims and study findings, represented the CDPH site on multiple TBESC committees, supervised multiple research assistants, and successfully facilitated record review and patient retention. Identified and overcame barriers as they arose and successfully tracked lab data. Her TBESC research coordination experience has spanned a retrospective study of TB deaths across 16 California jurisdictions (n=448 cases and 448 controls); TB HIV cases in 2 California clinics (n=300); Retrospective cohort study of MDR TB treatment (n=78); Prospective study of MDR transmission (n=55) involved all California jurisdictions and the Cohort study of LTBI adherence (n=170). As lead epidemiologist for the tuberculosis study on missed opportunities among the foreign-born she directed recruitment of 262 patients between 2004 and 2007, data collection, quality assurance and interview instrument pilot and development. She monitored milestones for meeting study objectives and ensured timely and accurate reporting to CDC.

Local TB Program Partners

Co-Investigators

Three California TB controllers, Dr. Kathleen Moser, Dr. Julie Low, and Dr. Masae Kawamura are proposed as co-investigators. Each of these TB controllers has nearly 2 decades of clinical and programmatic experience in identifying and treating persons with TB and LTBI. All three TB controllers will contribute as a local site co-investigator for the TBESC studies. These controllers are nationally recognized subject matter experts in tuberculosis infection and disease diagnosis and treatment and serve regularly as faculty for national training courses. They have substantial experience in population TB control efforts and individual TB care. Each operates a high morbidity TB Control Program and high volume categorical TB clinic. The TB program in each of these jurisdictions focuses case detection and prevention efforts on persons at high risk for developing disease. In each clinic setting, the full spectrum of high risk groups targeted for this study are examined and treated including HIV-infected, close contacts, immunocompromised, children, and new and remote foreign-born immigrant and refugee arrivers. In addition, drug - using and homeless populations are a significant population in each of these jurisdictions. All three controllers have extensive experience in managing immunocompromised patients with active TB and LTBI, in addition to managing TB outbreaks in high risk and clinical complex populations.

In addition to extensive clinical and programmatic experience, each controller has a successful track record in directing recruitment and enrollment of individuals in studies of LTBI diagnosis and treatment both as a part of TBESC, TBTC, the National Institutes of Health (NIH), and other local studies.

San Diego County TB Control Program and Public Health Laboratory

Dr. Kathleen Moser, Chief of Tuberculosis Control and Border Health Services in San Diego County, has led a highly effective tuberculosis control program in a jurisdiction that borders Mexico. Dr. Moser will devote 0.05 FTE (2 hours weekly) to this project. Dr. Moser received her medical degree at the Medical College of Pennsylvania, completed residencies in preventive medicine and internal medicine, and received a Masters in Public Health degree from Harvard School of Public Health. She has served on the National TB Controllers Association executive committee, the steering committee of the Strategic Plan for TB Education and Training, the Advisory Council for the Elimination of TB, the steering committee of the San Diego TB Elimination Task Force, and is a past president of the California TB Controllers Association. Under the direction of Dr. Moser, San Diego TB Control Program in collaboration with UCSD participated in the TB Clinical Trials consortium and successfully enrolled patients from the San Diego Department of Public Health TB Clinic for the QuantiFERON study, study 26, and other studies. She served as a co-investigator and primary collaborator for the past decade of TBESC research involving California and San Diego. She has published on predictors of treatment adherence and screening outcomes in immigrants and children. The program under her leadership has deployed an innovation for adherence, video DOT, for many years.

Dr. Marisa Moore, a CDC medical epidemiologist assigned to San Diego, has extensive experience in research design, data analysis, and data management and years of practical experience in operationalizing research in San Diego clinical setting. She served a key role at the San Diego site in facilitating the past decade of TBESC research in collaboration with CDPH study staff. She will support the San Diego study site by facilitating access to clinic data and providing input into protocols to ensure feasibility in the clinical setting. Dr. Moore will play a role

in interpretation of site analyses/study tracking activities that will be disseminated by the central Project Coordinator.

Dr. Patricia McVay, Chief of the San Diego County Public Health Laboratory, received her medical degree and training in Clinical Pathology at UC San Francisco and Master's degree in Microbiology at UC Los Angeles. She has 10 years' experience as Director in Blood Banking and Transfusion Medicine. Degrees include American Board of Pathology certification in Clinical Pathology and subspecialty board certification in Transfusion Medicine Dr. McVay will be responsible for directing the public health laboratory work including interferon gamma release assays for studies that enroll TB patients with LTBI from San Diego County.

Christine Kozic, Research Coordinator has MPH with concentration in epidemiology and extensive experience in protocol development, IRB submissions, data abstraction and collection for research studies. She will devote 0.50 FTE (20 hours weekly) to this project to perform data collection, quality control, tracking of enrollment and follow-up of patients, and enrollment backup activities for the Research Nurse Coordinator (see UCSD below).

University of California, San Diego

Dr. Richard Garfein is an Associate Professor with the Division of Global Public Health, Department of Medicine, UC San Diego. Dr. Garfein will devote 0.05 FTE (2 hours weekly) to this project. He has over 17 years' experience as an infectious disease epidemiologist conducting observational and interventional research to describe the epidemiology and test interventions to prevent transmission of infectious diseases among injection drug users (IDUs) and other marginalized populations. He is the principal investigator on the recently completed CDC-funded cross-sectional study of HIV and HCV infection among young adult IDUs in San Diego. He also has expertise in TB among marginalized populations in the U.S.-Mexico border region, which includes conducting the first ever QuantiFERON TB testing in Mexico to study the prevalence, incidence and risk factors for TB infection among 1,056 injection drug users in Tijuana as part of the NIDA-funded *Proyecto El Cuete* study. He is currently the principal investigator on a NIAID-funded R21 grant to design and test an intervention utilizing video-enabled cellular phones to monitor adherence to TB treatment in San Diego, CA and Tijuana, Mexico. His findings have been published in general and specialty peer-reviewed journals, and presented at national and international conferences. He received his BA at the University of California, Santa Barbara; PhD in Epidemiology at Johns Hopkins University, and served as a CDC EIS Fellow in Infectious Disease Epidemiology. He received the DHHS Secretary's Award for Distinguished Service, National Hepatitis C Recommendations Working Group and CDC Honor Award, Hepatitis C Inter-Center Working Group. He has extensive experience in studies that investigate LTBI prevalence, and innovative adherence strategies and use of IGRAs in hard to reach populations.

Constance A. Benson, MD (Co-Investigator). Dr. Benson is an internationally recognized HIV/AIDS researcher who has been involved in translational and clinical HIV/AIDS research for over twenty years. She has been active in the AIDS Clinical Trials Group (ACTG, funded by the National Institutes of Health) since 1987, and has served since 1991 in numerous scientific leadership and governance roles of this large, multicenter, multinational clinical trials organization. Dr. Benson has been the PI of the ACTG and Chair of its Executive Committee from 2003-2011. She has developed and chaired numerous ACTG protocols and has led other NIH/NIAID-sponsored projects. Dr. Benson has published extensively in peer reviewed journals including Annals of Internal Medicine, Antimicrobial Agents and Chemotherapy, Journal of the

American Medical Association, AIDS, Journal of Acquired Immune Deficiency Syndrome (JAIDS), Journal of Infectious Diseases, and Clinical Infectious Diseases. She serves on the scientific program committees of the Conference on Retroviruses and Opportunistic Infections and the International AIDS Society's International AIDS Conference, and has been invited to present her work at numerous international meetings. Dr. Benson's major research interests are in the treatment of HIV-1 related opportunistic infections (in particular tuberculosis and *Mycobacterium avium* complex), the pathogenesis and treatment of acute HIV-1 infection, complications of HIV therapies, evaluation of antiretroviral treatment strategies and new antiretroviral drug development, and capacity building and research training for HIV/AIDS in resource-limited international settings. In addition to her role as protocol chair on completed ACTG studies, Dr. Benson is the protocol chair of current ACTG studies A5001 and A5086, as well as a protocol team member/co-investigator of A5029 and A5217. Dr. Benson will assist with participant recruitment and retention oversight, and consult on data analysis, interpretation of results and dissemination of research findings. As Dr. Benson has other sources of funding, no salary support is required.

Julie Hoffman, Clinical Research Nurse is an experienced nurse who has coordinated clinical research studies at the University of California, San Diego's Antiviral Research Center for nine years. She will devote 0.50 FTE (20 hours weekly) to this project as the Research Nurse Coordinator responsible for patient enrollment and follow-up.

Delys Brooks, Phlebotomist and Laboratory Technician, is an experienced, certified phlebotomist who will devote 0.25 FTE (10 hours weekly) to perform venipuncture and collect, track, send specimens to the San Diego Public Health Laboratory, and to assist the Research Nurse Coordinator with subject recruitment, enrollment and follow-up activities.

San Francisco County TB Control Program and Public Health Laboratory

Dr. Masae Kawamura is TB Control Director of the San Francisco Department of Public Health. Dr. Kawamura will devote 0.10 FTE (4 hours weekly) in-kind to this project. She has served as Chair of the Advisory Council for TB Elimination and President of the North American Region for the International Union against TB and Lung Disease. She is Board certified in Internal Medicine and received her medical degree from the University of Hawaii and Bachelors of Science in Microbiology from the University of Washington. She has provided TB clinical care for nearly 20 years. As Assistant Clinical Professor of Medicine at the University of California San Francisco (UCSF) and Co-PI for Francis J Curry International TB Center, she is a nationally recognized expert in clinical care and TB control. Under her leadership she has led research efforts focused on latent TB infection and TB diagnostics and TB and LTBI treatment completion in high risk populations. She has published extensively on TB treatment outcomes, molecular epidemiology, and TB diagnostics. She has also published on TB prevention opportunities among the foreign-born, the feasibility, acceptability and cost of the whole-blood interferon-gamma assay. She has coauthored publications on the multicenter trial (SCRIPT) study of short course Rifampin and pyrazinamide (PZA) for TB infection and a cost-effectiveness analysis based on a multicenter trial of the short course rifampin and pyrazinamide compared with INH for latent TB infection. She has multiple publications on treatment adherence including a randomized controlled trial of interventions to improve follow-up for LTBI after release from jail.

Jennifer Grinsdale is the SF TB program epidemiologist and program manager. She received her Bachelor in Science in Molecular, Cellular and Developmental Biology from UC Santa Barbara and Masters in Public Health from the University of California Berkeley. She has

worked in the San Francisco TB program for over 10 years. She has been responsible for data integrity for the San Francisco TB registry and analysis and has contributed to the design and implementation of multiple studies utilizing TB patient data. She serves as Epidemiology faculty for the Curry International TB Center and has co-authored multiple publications on LTBI and TB diagnostics. Ms. Grinsdale will play a role in interpretation of site analyses/study tracking activities that will be disseminated by the central Project Coordinator.

TBD, Research Nurse Coordinator will devote 1.0 FTE (40 hours weekly) to this project and will be responsible for enrollment and follow-up of study participants, data collection and quality assurance activities.

TBD, Epidemiologist will devote 1.0 FTE (40 hours weekly) to this project and will perform data collection, enrollment and follow-up tracking, and quality control activities.

Dr. Mark Pandori is the Director of the San Francisco Public Health Laboratory and Associate Clinical Professor of Laboratory Medicine, UCSF. He has published extensively in microbiology and evaluation of infectious agent diagnostics including rapid TB diagnostics. He received his PHD in Biomedical Sciences at UCSD followed by postdoctoral research at Harvard where he also served as Instructor of Medicine at Harvard Medical School. He is Board Certified as a High Complexity Clinical Laboratory Director.

Orange County Health Care Services Agency TB Program and Public Health Laboratory

Dr. Julie Low is TB Controller for the Orange County Heath Care Agency and has worked in the TB Control Program for over a decade. Dr. Low will devote 0.10 FTE (4 hours weekly) in-kind to this project. She is board certified in Internal Medicine (2010-2020), Nephrology (1994-2004) and Geriatrics (1994-2004). She received her BA in Biology at Brown, MD at the University of Cincinnati College of Medicine, Ohio, and residency and fellowship at Kaiser, Los Angeles. She has served as President of the California TB Controllers Association, was an invited faculty at Curry International TB Center course "What Do We Know About LTBI?" and contributed as a Member of the CDPH/CTCA TB Contact Investigation Guidelines Group. She is in charge of the TB program with the second highest TB morbidity in California and had successfully managed medically complex outbreaks and contact investigations. As a researcher she has participated and consistently supported patient recruitment in Orange for numerous multisite studies during the past decade of TBESC.

Michael Carson is the Manager of the Pulmonary Diseases (TB Control Program) and Refugee Health Services in Orange County Health Care Agency. He holds an MS in Preventive Medicine and BS in Pre-Medicine and previously served as a CDC Public Health Advisor and Epidemiology Faculty in Irvine. He oversees the complex operations of the TB Program and provides epidemiologic capacity and data management for this program. He has coordinated IRB approvals, data access, patient recruitment, and provided key cost data for specific TBESC studies. Mr. Carson will play a role in interpretation of site analyses/study tracking activities that will be disseminated by the central Project Coordinator.

Richard Alexander is the Laboratory Director for the Orange County Public Health Laboratory. He is a certified Public Health Microbiologist and Clinical Laboratory Scientist. He received his BS in Microbiology and MS in Immunology at Cal Poly and MPH in Epidemiology at University of California Los Angeles. He has published extensively on infectious pathogen diagnostics and

has been an invited consultant for CDC to evaluate and train laboratory staff multiple international settings including in Ethiopia, Vietnam, South Africa, Ghana and Thailand. He also served as consultant to the Gates foundation in an evaluation of Potential Anti-mycobacterial Drug Testing Laboratories in Peru.

Randee Bautista, Supervising Public Health Nurse, has 14 years' experience with patients with LTBI and active TB disease. She will devote 1.0 FTE (40 hours weekly) as the Research Nurse Coordinator to enroll and follow-up study participants, and perform data collection and quality assurance activities.

Haimanot Girma, Senior Epidemiologist, has 11 years' experience as a public health epidemiologist. She will devote 0.50 FTE (20 hours weekly) to this project to perform data collection, quality control, tracking of enrollment and follow-up of patients.

B. Describe any previous relevant experience in similar projects

The CDPH TB Control Branch and partners from San Francisco, San Diego, and Orange each have substantial scientific experience and expertise in the development, implementation and analysis of research on LTBI evaluation, treatment and follow-up. This group has contributed to over 20 research studies focused on LTBI in the past decade and served key roles in research development, implementation and analysis. Selected research is presented in Appendix A and below.

CDPH TB Control Branch

CDPH TBCB led the development and analysis of four published studies investigating the cost effectiveness of latent TB infection evaluation and treatment. Each of these studies was conceived and implemented by a TBCB senior research scientist under the direction of the CDPH TBCB Principal Investigator. These studies began with a key scientific question, required extensive literature review, complex analysis and modeling, and culminated in publication, with subsequent key program and policy changes. To design and carry out these studies, including model construction, these studies required critical review of the literature on estimates on risk of LTBI to TB progression, risk of drug-related adverse events, including hospitalization, hepatitis and death. The studies also required original collection of data on costs of TB diagnostics and interventions to compute case prevention estimates. The detailed knowledge gained from these studies allows the proposed CDPH TBESC PI to make expert contributions to future studies on LTBI progression and diagnostics and costs proposed as the focus for the new consortium.

CDPH TB Control Branch has also demonstrated the ability to provide scientific expertise to research development, implementation and analysis as a member site the current TBESC. Our team has made important scientific contributions to ten studies conducted as part of TBESC, participating in the conceptual stage, in implementation, and analysis. The California site has participated in the following TBESC studies: Task Orders #3, #7, #8, #9, #13 (3 phases), #25, #28, #29, #33. For all studies, the CDPH site helped to define study design, develop and pilot study instruments, contributed to analysis and manuscripts. For the majority of these studies we contributed the largest study sample and shared with other sites our experience in successful data collection and overcoming key barriers. The CDPH PI served as co-PI for multisite studies: TO #8, #25, and #28. Each of these studies involved multiple US sites. We have provided significant scientific contributions to implementation and analysis of TO9, a cross-sectional study of foreign-born TB patients involving patient recruitment and interview. The CDPH study team participated in protocol development, piloted the data instrument, enrolled the largest patient sample of any site, and has provided an analysis of prevalent and incident disease

recently presented at the 2011 ATS meeting. The study focused on LTBI (TO13) entailed 3 phases and critical input on study design, study instrument development, pilot, analysis and publication by our study team. For TO# 25 and #28, the CDPH PI has served a lead role in collaboration with the CDC PI. CDPH developed the study concept for these two studies. For the mortality study, we contributed a data abstraction tool we had previously developed and piloted, as the basis for data collection for this study. We provided regular scientific and clinical input into the design, implementation and analysis of data. To inform implementation of the mortality study, we invited the CDC team to examine 25 records of TB deaths and assess TB relatedness and compare their assessments to previous evaluations in order to finalize the study plan. Most recently for TO #28, we developed the first draft of the analytic plan for multi-site input. As a study that grew out of TO#20, we have collaborated with CDC and Denver investigators to develop and evaluate a matching method using California TB case and overseas immigrant data. This matching methodology is anticipated to inform future matching of LTBI registries with case datasets for the TBESC. In summary, our scientific contributions to TBESC studies has ranged from developing the study concept and instruments, to contributing to all phases of design and study implementation, and providing analytic capacity for examining and presenting study outcomes.

San Francisco County TB Control Program

In the past decade, the SF TB program under the direction of Dr. Kawamura has participated in over 10 studies focused on latent TB infection diagnosis or treatment. These studies include over 5 clinical trials focused on treatment of TB and LTBI, 4 studies on diagnostics and multiple additional cohort studies focused on treatment outcomes and adherence (Appendix B). As a co-investigator or PI, Dr. Kawamura has contributed to original study concepts, provided critical review of study protocols and instruments, and contributed as a TB subject matter expert in the analysis and manuscript writing. She mentors a CDC medical epidemiologist and staff epidemiologist on-site who have led or contributed to the study design and analysis of multiple original studies. The two most recent studies focused on TB diagnostics include an analysis of the utility and cost of interferon gamma release assay and an ongoing assessment of the GeneXpert and impact on TB diagnosis and clinical outcomes. Dr. Kawamura and the San Francisco TB Program team have participated in CDC funded TB Clinical trials, the most recent including Study 26 and multiple other studies. Dr. Kawamura is an acknowledged national expert in TB, the PI of the Curry Regional Training Center, former chair of ACET, and president of North American Chapter of the International Union Against TB and Lung Disease (IUATLD). She is an invited consultant and coauthor of the most recent CDC IGRA Guidelines and provided numerous lectures on use of IGRA at national conferences. As a pioneer in evaluating new TB diagnostics, Dr. Kawamura has over 10 years of experience in use and systematic evaluation of IGRAs in a program setting. The scientific expertise and participation by the San Francisco TB program will greatly enhance and contribute to the new consortium.

San Diego County TB Control Program

Over the past decade, the San Diego program, under the leadership of the TB controller Dr. Moser, has participated in multiple TB studies focused on diagnosis and treatment. As a co-investigator or PI, she has played significant role in development, implementation, and analysis of numerous studies. Dr. Moser collaborated with UC San Diego investigators in several clinical trials and in multiple investigations of TB diagnostics. In TB Clinical trial, Study 26, as a local co-investigator, Dr. Moser, in collaboration with Dr. Phillip LoBue, facilitated recruitment of study patients. In two studies focused on LTBI diagnostics, she contributed a large sample of patients and coauthored associated publications. The San Diego program has participated and successfully supported the CDPH site in TBESC studies #3, 8, 9, 25, and 28, 33. For TBESC

studies both Dr. Moore and Dr. Moser have provided scientific input into study implementation and analysis.

University of California, San Diego (UCSD)

In addition to strong ties to HIV medical care providers in San Diego, the AVRC and Owen Clinic have close collaborations with non-medical community service organizations and their staff. These include HIV case managers, health educators, hospice care and recovery homes, HIV test counselors, and the San Diego County-UCSD Early Intervention Program (EIP) and Bridge Program. EIP is a county-sponsored program for identifying and transitioning patients newly diagnosed with HIV into care and clinical trials. The Bridge Program is responsible for "bridging" urgent care needs for the individuals enrolled into EIP into chronic care and follow-up. The latter program also follows up on patients who fall out of care, and provides resources to re-contact such patients and assist them to re-engage in care. Both are unique programs that work together to reduce loss-to-follow-up and facilitate retention in care, both for clinical care and for research studies. The EIP and Bridge programs are co-located at the AVRC facility, staffed by UCSD faculty and staff, and offer a broad range of opportunities to integrate HIV prevention interventions, clinical care and research.

Orange County TB Control Program

Under the leadership of Dr. Low, OCHCA has participated in multiple TBESC studies carried out in California including TO 9, 25, 28. The pilot of each study involved patient samples from Orange and Dr. Low provided critical feedback to the study instruments for each of these studies. Dr. Low and staff have recently participated in a study on the role of antibody proteomic arrays in LTBI diagnosis. This study in collaboration with Dr. Steven Park of UC Irvine Medical Center, evaluated the utility of *M.tb* antibody proteomic arrays in diagnosing latent TB infection and in monitoring TB treatment response in comparison to the TST and the IGRA. 250 patients with LTBI were enrolled and Dr. Low provided critical input into the pilot, study implementation and analysis. Dr. Low and her TB staff have successfully implemented over 5 TBESC studies and consistently contributed to high enrollments rates. Dr. Low recruited the CDPH on-site research assistant and has overseen the studies for over 5 years. This research assistant recruited and enrolled patients, abstracted records, performed data entry , performed quality assurance for 4 TBESC studies: TO #8,#9, #25, and #28. Dr. Low is expert in operationalizing studies, providing expert feedback on feasibility and pilot results, and strategizing study barriers as they arise. For the MDR TB treatment and practices study she provided feedback on data sources and data elements for the study protocol and the data collection instrument. She also reviewed the variables on cost and process for cost data collection. For a consortium focused on LTBI diagnosis and adherence and treatment she will contribute over a decade of direct patient care in one of the highest morbidity counties in the nation, ensuring this important study is pragmatic and leads to usable information for TB control efforts.

Experience conducting research studies

CDPH TBCB has a long history of conducting productive research of public health relevance. In the current 10 year TBESC research consortium, CDPH TBCB has participated in 10 multi-site research studies which include TO#3, TO#7, TO#8, TO9, TO#13- phase 1-3, TO#25, #28 and #29. As an extension of study TO#20, CDPH has also recently successfully partnered with the Denver site and CDC to carry out the overseas linkage study. The completed TBESC studies include TO#3, #7, #8, #9, and #13. For the most recently awarded studies, TO# 25, #28, and #29, data collection and analysis is in their final stage. For each of these studies, the CDPH site has consistently contributed the largest patient sample. The CDPH study team also contributed as coauthors for publications for TO#3, #7, and #13. Abstracts, presentations, and manuscript

drafts have been completed for TO #8, #9, and #25. Our study team has provided extensive analysis and data interpretation for several presentations and abstracts for TO#9. We are actively participating in the author group for two TO#9 manuscripts. Most recently, an analytic plan and manuscript outline was developed for TO#28 by the CDPH PI and senior research scientist for review by the multisite team.

The proposed CDPH PI, Dr. Flood, has served as a co-investigator for multisite studies on diagnostic and treatment research related to sexually transmitted diseases and unexplained infectious pathogens prior to her TB position. She directed the San Francisco site enrollment in a trial of early syphilis and HIV and completed multiple studies including studies on chancroid, neurosyphilis, and on chlamydia and genital ulcer diagnostics. In addition, she led the California site participation in the CDC funded Unexplained Illness Study which culminated in two publications and a study on CMV diagnostics.

CDPH, with Dr. Flood as Principal Investigator, has also received CDC funding and successfully completed five enhanced TB surveillance and evaluation projects culminating in peer-reviewed publications and presentations at national forums. These include: a 5 year genotyping surveillance study (NTSGN),a systematic evaluation project of contact investigation, an evaluation of latent TB infection targeted testing and treatment, an enhanced MDR/XDR TB surveillance project, and an evaluation of HIV testing among TB patients.

CDPH TBCB has successfully partnered with academic collaborators from UCSF, UCD, and UCSD on NIH studies. The NIH studies currently in progress which include Dr. Flood as a co-investigator include research in partnership with UCSF, UCSD, and UCD. Specifically, Dr. Flood has served as a co-investigator for two completed NIH-funded studies on TB treatment outcomes and drug resistance and three studies in progress.

San Francisco, Orange and San Diego TB Control Programs:

Conducting studies TBESC, TBTC, NIH
Our California partners, San Francisco, Orange and San Diego have participated in multiple TBESC studies, including TO#3 (San Diego), TO#8 (all),TO#9 (all),TO#25(all); TO#28 (all). In addition San Diego and San Francisco TB Programs are participating in TO#33. TBTC trials and NIH studies have also been collaboration with the San Francisco and San Diego TB programs. Original research has been conceived and implemented leading to landmark publications in molecular epidemiology and TB diagnostics as well as research investigating outcomes of special populations drug users, MDR TB, *M.bovis*, HIV-infected.

Productivity: Completed Studies

The CDPH has partnered with CDC and multiple U.S. sites to successfully complete eight TBESC studies. These completed studies include TO#3, #7, #8, #9, and #13- 3 phases. CDPH with TBESC collaborators are currently in the process of completing 3 of the consortium's last studies TO#25, #28, and #29. CDPH contributed the highest number of study subjects in virtually every study in which we participated. We exceeded enrollment targets in 2 studies (TO#13 and T0 #9). Of note, all three of our proposed partnering sites (SD, SF, and Orange) participated in TO# 9 and contributed large patient numbers.

In addition to TBESC studies, CDPH TBCB has completed numerous additional studies that are relevant to this consortium's focus: studies on LTBI, TB diagnostics, and studies of cohort outcomes. TBCB has completed 4 studies on TB diagnostics including a study on impact of

rapid drug resistant assays, diagnosis of TB meningitis, laboratory testing and reporting, and IGRA in renal dialysis centers.

The San Francisco and San Diego County TB Control Program partners have participated in numerous TB Clinical trials as part of the CDC TBTC. These include study 26 and 28. Drs. Moser, Kawamura, and Moore, and Dr. LoBue facilitated study enrollment and contributed to the successful outcome and contribution by TB programs to these trials. Publications from the completed trails involving San Diego and San Francisco TB clinic sites include multiple TBTC publications. The San Francisco and San Diego County TB Control Programs also have been highly productive in completing original research. Many of these studies focused on TB diagnostics, LTBI, or TB cohort outcomes and are detailed below.

The Orange County TB Control Program

The OCHCS TB Program as a collaborator of CDPH TBCB contributed patients and data collection for TO #9, TO #25, and TO #28, In addition, this program partnered with UC Irvine investigators to evaluate the role of proteomics in LTBI and TB diagnosis and treatment response.

San Francisco County TB Control Program

The San Francisco TB Control Program participated in the following multisite TBESC studies: TO #9, TO #25, and TO #28, and TO#33. In addition, they have served as co-investigators in TBTC study 26 and other TBTC studies. The San Francisco TB Control program has also carried out and published original research, independently as well as in collaboration with UCSF researchers, on a wide range of topics from TB diagnostics including GeneXpert technology, IGRAs, and the molecular epidemiology of TB.

San Diego County TB Control Program

The San Diego TB program has enrolled patients in diverse studies and has consistently demonstrated high enrollment rates. San Diego participated as a collaborator for the CDPH TBESC site in multiple TBESC studies including TO#3, #8, #9, #25, #28, and #31. Patient enrollment for TO#9 included approach, consent, enrollment, and in-depth interview of active TB case patients. A large number of patients were successfully enrolled from this site during the study period.The San Diego clinic has also been a successful study site for numerous studies involving TB diagnostic tests. The clinic participated in a multi-center prospective trial evaluating performance of the amplified MTD test and successfully contributed a high number of study subjects for several Tuberculosis Clinical Trials Consortium studies. The CDC funded QuantiFERON TB study examined the utility of the first generation IGRA as a new diagnostic test for LTBI. The San Diego study site enrolled 297 patients – the highest patient enrollment of any of the 5 study sites for this study.

Dr. Moser has served as Principal Investigator for the Border State Study to determine demographics, treatment, and movement patterns of Hispanic TB patients. As part of this multi-site study, under Dr. Moser's direction, the San Diego site approached, enrolled and interviewed 78 patients, the largest number of any site. Additionally, Dr. Moser and Dr. Chris Peter, Director of San Diego Public Health TB laboratory, served as co-principal investigators in a multi-center study funded by Genprobe to determine performance characteristics of the MTD2 test for the diagnosis of active TB.

UCSD

Dr. Garfein, in collaboration with Dr. Benson, will direct enrollment of HIV-infected participants through the UCSD AVRC and Owen Clinic. The AVRC has completed more than 250 clinical

trials since its inception, with an average annual enrollment of 100-125 patients, and an average monthly census of more than 350 patients followed on study. Total enrollment in HIV/AIDS clinical trials in its 23-year history is well over 2,000 patients. Dr. Benson's clinical trial experience within the last 5 years relevant to this application include serving as the PI and Chair of the Executive Committee of the NIH/NIAID AIDS Clinical Trials Group (ACTG) from 2003 to the present, as well as Chair of the ACTG's Scientific Agenda Steering Committee from 1996-2003. In that role she has had extensive experience in the scientific and organizational administration of a large multi-center, multi-national clinical trials network comprising more than 75 clinical research sites and laboratories in 15 different countries.

Productivity: Previous Publications

Over 40 TB related studies have been published by CDPH TBCB authors since 1995 – The proposed TBESC CDPH site principal investigator, Dr. Jennifer Flood has published extensively on research related to TB and other infectious pathogens (Appendix E). Several landmark publications have included: effect of a screening program on domestic TB (Lowenthal), impact of rapid drug resistance assays, and cost-effectiveness of TB evaluations of new immigrants.

The San Francisco TB program has a prolific research publication record with numerous publications on TB in past 10 years; Similarly San Diego has published numerous articles on topics spanning from *M bovis*, to lab testing to treatment adherence. In summary, the CDPH TBCB and its TB clinic partner sites have extensive experience in conducting research. The proposed PI has over 15 years' experience serving as principal investigator and co-investigator in multi-site CDC and NIH studies with successful outcomes culminating in publications. CDPH TBCB publications in the past 15 years include studies focused on TB diagnostics, LTBI and outcome of TB patient cohorts; San Francisco, orange and San Diego TB programs have conducted numerous research studies, including those within the TBESC, and TBTC. Please see Appendix A for a list of selected research studies performed by CDPH TBCB and partner sites.

Productivity: Scientific Accomplishments

The proposed research team composed of CDPH PI, director, PC and co-investigators have made significant contributions to TB control in scientific leadership and are not only subject matter experts but regularly sought for key scientific roles on evidence-based treatment and diagnostic guidelines, national advisory committees, as journal reviewers, and mentors for a range of scholars.

Dr. Jennifer Flood recently served as an invited consultant on a CDC advisory committee charged with advising CDC on formulating recommendations on implementing the 12 dose rifapentine INH regimen. She served for 4 years as a member of CDC's Advisory Council for TB Elimination. And is a President elect for the National Society of TB clinicians as well as an NTCA Executive Board member representing High Morbidity TB states. She has been an invited Consultant to CDC teams charged with evaluation of TB screening programs in Nepal and Vietnam. She previously served as consultant on CDC Team to investigate an increase in MDR TB in Armenia.

As a member of TBESC, she was elected to serve on TBESC research committee member for 4 years. She was also the recipient of several awards in TB control including the Renteln award; and superior accomplishment award. She has mentored numerous UCB, UCD, UCSF MPH, MD, PHD , CDC Preventive Medicine, EIS, CSTE fellows and students in completing original

research and has served on public health doctoral student dissertation committees. Her scientific accomplishments in TB control are also evidenced in the large number of invitations received as a keynote speaker at scientific conferences. Finally, she is a reviewer for AJPH, IJTLD, and CID.

Dr. Lisa Pascopella was elected to the TBESC Translating Research into Practice Committee and served as co-chair 2007-2008; also elected to the TBESC Research Committee and served for 5 years. Her publication record is listed in her biosketch, (see Appendix C).

Katya Salcedo received an award as the most successful TBESC project Coordinator award in 2006.

Drs. Masae Kawamura and Kathleen Moser also have been nominated to contribute their scientific expertise as part of national committees, guideline members or councils on TB control. Dr. Kawamura served as Chair for ACET, contributed as a member and writer for the most recent of the CDC IGRA Guidelines, contributed to multiple other evidence-based TB treatment and diagnostics guidelines including the CDPH/CTCA e TB treatment and B-notification guidelines. She is a recipient of the Henry Renteln award and PI of the Francis J Curry Regional and Training Center as well as Past president of North American IUATLD.

Dr. Richard Garfein has been the principal investigator on many completed CDC and NIH studies related to HIV, HCV and TB and innovative treatment adherence strategies. He also implemented the first ever QuantiFERON TB testing in Mexico to study the prevalence, incidence and risk factors for TB infection among 1,056 injection drug users in Tijuana as part of the NIDA-funded *Proyecto El Cuete* study. He was awarded the DHHS Secretary's Award for Distinguished Service, National Hepatitis C Recommendations Working Group. He also received a CDC Honor award for work with the Hepatitis C Inter-Center Working Group. He has received research support for multiple CDC, NIH, and USAID studies in the role of principal investigator

Dr. Mark Pandori has received multiple awards including the Morrison Research Award and the Fleischener Award, Beth Israel Deaconess Medical Center, Boston, MA. He has published numerous ground-breaking investigations of HIV and STD molecular diagnostics(p. 3 of selected publication (Pandori, JClin Microbiol 2009) and published one of the first evaluations of the Cepheid Xpert MTB/RIF assay in a U.S. population.

C. Provide a detailed work plan showing a table of activities and outcomes, along with a proposed timeline for each activity

Table 2. WORKPLAN TABLE OF ACTIVITIES AND OUTCOMES

Period	Activities	Outcomes
Base period (6 mos) Sept. 2011- Mar. 2012	• Review protocol • Suggest possible modifications, improvements to protocol, and provide feedback on practicality and feasibility	Study protocol and study forms will be drafted in near-final form Study support staff at each site (San Francisco (SF), Orange (Or), San Diego (SD)) will be hired
Option period 1 (6 mos) Mar. 2012-	• Obtain IRB approval (local or deferral to CDC)	All IRB approvals will be garnered CDPH TBCB central and site-specific (i.e. SF, Or, SD) implementation plans

Period	Activities	Outcomes
Sept 2012	• Prepare implementation plan and pilot test • Step-by-step plan for protocol implementation, including: o Staffing, materials, and confidentiality requirements o Patient recruitment and enrollment o Data collection, entry, quality control and assurance o Patient F/U at 6, 12, 18 & 24 mos after LTBI dx o Methods for IGRA blood sample collection, processing, interpretation o Methods for TST placement and interpretation o Methods for obtaining and storing patient serum • Pilot test of study o Enroll 50 patients o After pilot is completed, discuss with CDC whether modifications to the protocol are needed.	will be developed Study nurses in SF, Or, SD will be hired and trained 50 patients will be enrolled in pilot Recommendations for study modification (forms/processes/procedures) based on pilot findings will be submitted to CDC PI
Option period 2 (1 yr) Sept 2012-Sept 2013	• Begin LTBI patient enrollment, preventive treatment, follow-up, observation, data collection and analysis • Complete study forms for patients who refuse participation, and for patients who agree to participate in the study	Implementation plans finalized in response to final study protocol (modified by CDC in response to pilot findings). 750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and

Period	Activities	Outcomes
	• For participating patients: ○ Obtain blood for IGRA testing, serum for serum bank, apply, read TST and record TST results ○ For LTBI patients: complete all required study forms, offer LTBI Rx, follow up & complete form 1x/month for those on Rx, and meet & complete study form at 6, 12, 18 & 24 mos visits ○ At COT: repeat QFT test, complete study forms (and form at 2 yr F/U period) ○ Enter or upload data to CDC, submit monthly CDC cumulative summary form ○ Collect cost-related data	economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 3 (1 yr) Sept 2013-Sept 2014	• Continue conducting study as described in option period 2 • Focus on recruiting special LTBI populations • Participate fully as a member of the TBESC	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-up (n=375) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 4 (1 yr) Sept 2014-Sept. 2015	• Continue conducting study as described in option period 2 • Focus on recruiting	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient

Period	Activities	Outcomes
	special LTBI populations • Participate fully as a member of the TBESC	data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-up (n=750) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 5 (1 yr) Sept 2015- Sept 2016	• Continue conducting study as described in option period 2 • Focus on recruiting special LTBI populations • Participate fully as a member of the TBESC	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-up (n=750) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 6 (1 yr) Sept 2016- Sept 2017	• Continue conducting study as described in option period 2 • Focus on recruiting special LTBI populations • Participate fully as a member of the TBESC	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-up (n=750) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 7 (1 yr) Sept 2017- Sept 2018	• Continue conducting study as described in option period 2 • Focus on recruiting special LTBI populations • Participate fully as a member of the TBESC	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-

Period	Activities	Outcomes
		up (n=750) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 8 (1 yr) Sept 2018- Sept 2019	• Continue conducting study as described in option period 2 • Focus on recruiting special LTBI populations • Participate fully as a member of the TBESC	750 high-risk patients with LTBI and 750 high-risk patients without LTBI enrolled (=1500) Complete and accurate individual patient data forms and monthly cumulative summary forms submitted to CDC Complete and accurate close-out forms for all patients completing 2-year follow-up (n=750) submitted to CDC Retrospective and prospective data for comparative effectiveness, outcome, and economic analyses submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 9 (1 yr) Sept 2019- Sept 2020	• Begin to close down study (no new enrollments) • Continue to participate fully in TBESC	Complete and accurate close-out forms for all patients completing 2-year follow-up (n=750) submitted to CDC Ongoing participation in semi-annual consortium meetings and consortium committees
Option period 10 (1 yr) Sept 2020- Sept 2021	• Finalize study close down • Perform final data (lab & clinical) QA, clean up, and finalize site-specific dataset for main diagnosis study • Prepare final report for CDC • Continue to participate fully in TBESC	Complete and accurate close-out forms for all patients completing 2-year follow-up (n=375) submitted to CDC Finalized dataset completed and submitted to CDC Final study report submitted to CDC Completed participation in semi-annual consortium meetings and consortium committees

D. Describe the relationship between the site and the clinics that will be providing therapy or follow-up of enrolled LTBI patients? What capacity does the applicant have to recruit, test and collect data on the cohort of patients proposed for study?

CDPH TBCB is the lead agency in the state responsible for TB control. In carrying out this responsibility, CDPH TBCB provides technical and financial assistance to each of the proposed clinics in the form of :

- field assistance to investigate outbreaks and help local TB programs fill programmatic gaps that allowed TB to spread
- oversee the care of all multidrug resistant (MDR) and extensively drug resistant (XDR) TB cases and their contacts to prevent spread of these deadliest strains

- work with local programs to evaluate and improve performance on key TB control indicators (TB Indicators Project, TIP)
- collect data and conduct studies to evaluate and guide TB control interventions
- ensure fiscal accountability and efficient application of resources to highest priority needs of the state and local TB programs

CDPH TBCB has a longstanding and ongoing collegial relationship with all three local TB control programs and has a long history of successful research partnerships with proposed clinics. Each of these clinics has worked with CDPH TBCB in Task Orders 8, 9, 25 and 28, as well as other research studies (HIV status among TB patients, adverse treatment outcomes study, and others). As evidenced by this successful history, CDPH TBCB has the capacity to partner with each of the clinics proposed to participate in the consortium; it has garnered letters of collaboration.

At each local program, the TB controller is the medical director for the categorical TB clinics where study participants will be recruited and as such have the capacity to recruit patients from those clinics for study participation. The other collaborating clinics (HIV Clinic in San Diego and the Refugee and HIV Clinics in Orange) are managed by close collaborators of the local TB program who have granted access to the clinic populations for purposes of recruiting study participants. San Diego has a long-established research relationship with Drs. Benson and Garfein at the Antiviral Research Center at University of California San Diego, who will be partnering with the San Diego TB program to perform this study. Letters of collaboration have been obtained from all clinic partners (Appendix D).

E. **Describe the procedures necessary for collaborating clinic to alter their normal procedures to those specified in the CDC protocol, e.g. modify method of diagnosing LTBI (e.g. adding IGRAs if not currently using), to change your current LTBI preventive therapy regimen (e.g. addition of short course therapy), to modify the current methods of providing LTBI preventive therapy (e.g. adding directly observed preventive therapy)**

The TB controller for each of the three TB programs is directly responsible for and has authority for making any changes needed in clinic standard operating procedures. There are no other required approvals in each of the participating TB clinics. Modification of operating procedures at the clinics will be disseminated to staff, accompanied by training of staff after study protocol/procedures are finalized. For example, the standard operating procedure for a subset of patients who are evaluated in the TB clinic in San Francisco includes a QFT-GIT test. Since the study will require placement of tuberculin skin test (TST) in addition to collection of blood for the QFT-GIT, the TB controller will direct clinic staff to place and read TSTs on study participants, or, will inform clinic staff that study staff will be performing these tasks on all enrolled patients. In San Diego, the TB controller has authority over the refugee clinic, which is located about 10 miles from the TB clinic. The County of Orange Health Care Agency has two TB clinics, one located in Santa Ana and one in Westminster. The Refugee Health Services Clinic is located in Westminster, in the same suite as the TB clinic. The HIV clinic is located in Santa Ana, next door to the TB clinic, The TB Medical Director has authority over the TB and Refugee Clinic. In San Francisco, the TB controller also has direct authority to modify procedures and protocols. In Orange and San Diego sites, the TB controllers will work with the HIV clinic medical directors to ensure that client screening and follow-up procedures are congruent with study procedures. Each of the HIV clinic medical directors provided a letter of collaboration (see Appendix C).

Each participating clinic has been using QFT-GIT during patient evaluation for some groups of patients with LTBI for at least two years. Each clinic will incorporate the addition of placing a TST on each patient enrolled in the study, soon after venipuncture for QFT-GIT, and according to study protocol. Each participating clinic proposes the integration of current clinic staff processes with future research studies; including the referral of LTBI patients to study staff for enrollment; the inclusion of patient incentives and enablers and/or modified directly observed therapy to encourage treatment completion and follow-up among study participants; and additional tracking processes to ensure follow-up activities for study participants. Each of these clinics has experience using directly observed preventive therapy for a subset of high-risk patients (see above); addition of DOPT for groups not currently receiving DOPT would be easily incorporated into current clinic processes. Each clinic has had experience with a variety of treatment regimens for LTBI. In fact, two of three clinics have participated in the Tuberculosis Clinical Trials Consortium, including study 26, which evaluated the use of the short-course isoniazid rifapentine regimen for LTBI. These experiences provide evidence for the capacity to incorporate a new treatment regimen for LTBI in study clinics.

F. Discussion of facilities and equipment proposed for use under the task order at all participating sites

Clinic Sites

Each clinic site has the equipment and facilities necessary to carry out the proposed study. In particular, each clinic has TB skin testing equipment, radiographic equipment, sputum induction facilities, and phlebotomy equipment on-site. Laboratory equipment for collection of specimens for sputum smear and culture are also available on-site. Additionally, computers and network access will be needed for study staff (and is reflected in the Business Proposal). Detailed descriptions of the individual clinic sites are below:

The San Francisco County TB Control Program operates a single dedicated TB clinic. The clinic is located on the campus of San Francisco General Hospital The San Francisco TB Clinic is open Monday through Friday 8-5pm with drop-in and follow-up appointments scheduled. It has a reception area for registration and chart storage, a waiting room, interview room, 4 exam rooms, a sputum induction booth, phlebotomy station, pharmacy, and drug dispensing station and multiple staff offices. It is staffed by 10 nurses and 6 physicians, a social worker, multiple interpreters, clerks, information technician, program manager, physician liaison, and epidemiologist. The nurses perform phlebotomy. They also perform symptom review and drug adverse effect monitoring monthly, and dispense drug refills for patients with LTBI. Chest radiographs are obtained on campus at the hospital facility. Chest films are completed within 1-2 hours of physician order, and digitally transmitted back to the physician, so the patient can return to the clinic for clinician visit or disposition. Blood and sputum are transported to the public health lab by courier.

The Orange County TB Control Program operates two TB clinics: One located in Westminster and one in Santa Ana. The Refugee Health Services Clinic is located in Westminster, in the same suite as the TB Clinic. The HIV Clinic is located in Santa Ana, next door to the TB Clinic. The TB Program Management staff is located in Santa Ana in the same building as the TB Clinic. All TB and refugee clinics are open daily 8-4pm, with scheduled and drop-in appointments at the TB clinics, and scheduled appointments only at the Refugee Clinic.

The San Diego TB Control Program operates a dedicated TB clinic and provides a range of services including sputum collection, tuberculin skin tests, QFT-GIT and chest x-rays. Additionally, the program provides treatment for LTBI and active disease. The San Diego TB

clinic has three exam rooms, sputum foyer, two sputum booths, two isolation rooms, and an x-ray suite. The clinic is staffed by one fulltime physician, one registered nurse, three licensed vocational nurses, two x-ray technicians and a supervising public health nurse. There is a pediatric specialty clinic monthly staffed by rotating physicians from Rady's Children's Hospital. Hours of the San Diego TB Clinic are 8am-4pm Monday through Friday. The refugee clinic in San Diego consists of two exam cubicles in an exam room, a nurse station, and a blood draw room. This daily clinic is staffed by an attending physician from UCSD (often with a few residents from the UCSD School of Medicine) or nurse practitioner (from the TB clinic, who performs general health exams as well as LTBI treatment), one registered nurse, one phlebotomist, and two interpreters. The attending physician position is currently on a rotation among three providers under contract from UCSD.

University of California, San Diego clinicians see HIV-infected patients at 1) the Owen Clinic, which is located in the UCSD Medical Center Hillcrest Medical Office Building adjacent to the UCSD Hillcrest Hospital 3.2 miles from the San Diego TB Control Program; and 2) the Division of Infectious Diseases Outpatient Clinics, which are held in the UCSD Medical Center Outpatient Clinic or in the UCSD Thornton Perlman Pavilion Outpatient Clinic on the La Jolla/Thornton campus 10 miles from the San Diego TB Clinic. All clinics provide TB screening by TST and QFT-GIT, as well as treatment for active TB and LTBI. The combined total of patients seen per day in the UCSD Owen and ID clinics is 100-120. The Owen Clinic alone sees over 4,000 patients per year. The Owen clinic is open from 8 am-5 pm Monday through Friday.

Laboratory Facilities

Laboratory testing for the study including IGRA, AFB smears, cultures, and drug susceptibility testing are performed at the local public health lab. For this study, we are requesting that costs of QFT-GIT kits and processing of blood samples to perform and interpret QFT-GIT tests be reimbursed (as described in the Business Proposal). Detailed descriptions of each individual lab is below:

The San Francisco Department of Public Health Laboratory (SFDPHL)
SFDPHL is a state-of-the-art microbiology laboratory under the jurisdiction of the City and County of San Francisco. The SFDPHL facility encompasses over 4600 square feet of laboratory space, and is equipped with 5 class II biosafety cabinets, 2 robotic DNA/RNA extraction units, EIA testing equipment (for automated and manual execution), 2 rapid thermocyclers (for PCR), freezers (3x -80°C, 7x -35°C) for the storage of blood and other specimens, and 15 centrifuges for both clinical and molecular operations.

Approximately 120,000 lab tests are performed annually at the SFDPHL, which is staffed by 20 laboratory personnel, 10 of whom are bachelor's-level laboratorians who have been trained and certified by the State of California as Public Health Microbiologists, 1 of whom is a doctorate level scientist. The SFDPHL is fully equipped with over 20 personal computers connected by intranet that are continually staffed by certified network professionals. The SFDPHL has proximity to numerous support facilities, including San Francisco General Hospital, UCSF and UC Berkeley, with whom numerous collaborations take place on a regular basis. The laboratory is funded in part through the City general fund, in addition to a number of federal and state granting sources.

SFDPHL has been performing QFT testing (first generation and subsequent versions) since late 2003 and QFT-GIT testing from 2008 to present. The laboratory and the TB clinic have a long-established relationship. To-date the laboratory has done over 50,000 QFT tests, including approximately 10,000 QFT-IT tests per year. In 2009, the SFDPHL performed 10,329 QFT tests using an automated immunoassay processing device—a DSX Automated ELISA System by Dynex instruments, 2460 smears and cultures for AFB isolation. Between April of 2010 and April of 2011, the lab performed 187 NAA tests for MTB. All QFT testing at SFDPHL is performed by licensed (CA State Certified) Public Health Microbiologists. These staff are evaluated annually for bench level performance, and also perform proficiency testing using panels both internal and provided externally.

Orange County Public Health Laboratory

QFT-GIT tests are performed in the Immunology section of the Orange County Public Health Laboratory by certified Public Health Microbiologists. In 2010, 1373 QFT-GIT tests were performed, in addition to 5830 acid fast bacilli smears, 5880 cultures and 547 nucleic acid amplification tests (NAATs), 214 genotyping, and 82 drug sensitivity tests from specimens of patients suspected to have TB. This laboratory is a biosafety level-2 facility that uses a Thermo Wellwash 4MK2 plate washer and a Biotech ELX 800 plate reader to perform QFT-GIT. The laboratory has been performing QFT-GIT testing since April 2009. The laboratory is located across the parking lot from the Santa Ana TB Clinic and 5.73 miles from the Westminster TB Clinic.

San Diego County Public Health Laboratory

QFT-GIT tests are performed in the County of San Diego Public Health Lab by State of California certified Public Health Microbiologists. The laboratory implemented QFT-Gold in late 2006, and QFT-GIT in August 2008, QFT-GIT is performed using the Dynex DSX Automated System under BSL-2 conditions. All TB specimen processing and culture work is done in the BSL-3 lab. In 2009 the laboratory performed approximately 3200 QFT-GIT tests and 3800 TB cultures.

November 2, 2011

Barbara Garcia, M.P.A.
Health Officer
San Francisco Department of Public Health
Public Health
101 Grove Street, Room 308
San Francisco, CA 94110

Dear Ms. Garcia:

LETTER OF AWARD – San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies (TBESC) Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection"
FUNDING PERIOD – November 1, 2011 through September 28, 2012

This letter supersedes the Letter of Award dated October 14, 2011. The purpose of re-issuing this letter is to augment Task Order 1 to provide out-of-state travel funds so that the San Francisco County Principal Investigator, L. Masae Kawamura, M.D., may attend the first semi-annual TBESC meeting. The meeting will be held December 8 and 9 in Atlanta, Georgia.

AWARD

The California Department of Public Health (CDPH) Tuberculosis Control Branch (TBCB) is awarding the San Francisco Department of Public Health up to $23,538 to support this study. These funds are being awarded with the understanding that your staff identified in this award will work with the staff of the TBCB in carrying out study efforts.

This award is valid and enforceable only if 2012 Federal budget provides sufficient funds available for the purposes of this study.

MANAGING YOUR AWARD

Requirements for the use of these funds are listed in the enclosed Scope of Work, Budget and Part 1 of the FY 2011-2012 Policies and Procedures Manual (PPM). This manual can be found on the CDPH TBCB internet site at: http://www.cdph.ca.gov/programs/tb/Pages/LocalAssistanceAward.aspx. Reimbursement of your expenditures is contingent upon compliance with these

standards and procedures. The only exception to the PPM requirements for this award is that invoices for this study may be submitted monthly rather than quarterly.

Invoicing for your Award

A signed original invoice (in blue ink) must be submitted on your organization's letterhead. Bill to the California Department of Public Health, Tuberculosis Control Branch. Mail invoices to:

California Department of Public Health
Tuberculosis Control Branch
850 Marina Bay Parkway, Building P, 2nd Floor
Richmond, CA 94804-6403
Attn: Mr. David Beers, Fiscal Analyst

Invoices for this study will not be processed until a signed "Acceptance of Award" has been received by the CDPH TBCB.

ACCEPTANCE OF YOUR AWARD
To acknowledge your acceptance of this award and the conditions attached to it, please return an original of the attached "Acceptance of Award" with an authorized signature to:

California Department of Public Health
Tuberculosis Control Branch
850 Marina Bay Parkway, Building P, 2nd Floor
Richmond, CA 94804-6403
Attn: Mr. David Beers, Fiscal Analyst

Fiscal questions should be directed to the TBCB fiscal analyst, Mr. David Beers, (510) 620-3012 or by e-mail at david.beers@cdph.ca.gov. Study related questions should be directed to Lisa Pascopella, (510) 620-3865 or by e-mail at lisa.pascopella@cdph.ca.gov.

Sincerely,

Sue Spieldenner, RN, MPH, Chief
Resources Planning & Management Section

Enclosures: Award Acceptance Form
Scope of Work
Budget

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies Task Order 1
Scope of Work

1. Service Overview

Contractor agrees to provide to the services described herein.

Tuberculosis (TB) elimination remains a public health priority both nationally and in the state of California. California reports the greatest number of TB cases in the United States (U.S.) and the largest number of drug resistant cases. Nearly 10% of individuals diagnosed with TB disease in California die from TB-related causes. Successful strategies have been implemented to decrease the burden of TB since the disease's resurgence in the late 1980s and early 1990s. However, in order to reach elimination, in addition to identifying and treating persons with TB disease, TB control efforts must focus on reducing the large reservoir of potential future TB cases among persons with latent tuberculosis infection (LTBI), a population estimated to be 11 million persons residing in the U.S. and 2.3 million in California.

To further TB control and elimination efforts in California, the California Department of Public Health (CDPH) Tuberculosis Control Branch (TBCB), in collaboration with the San Francisco Department of Public Health TB Control Section participates as a selected study site in the Centers for Disease Control and Prevention (CDC) Tuberculosis Epidemiologic Studies Consortium (TBESC). Competitively selected TBESC sites carry out studies related to TB control activities. Each CDC study is assigned a specific number. Over the lifespan of the Consortium, all sites participate in Study #1 "Improving the Diagnosis and Treatment of Latent TB Infection." In addition, sites may apply periodically for individual, smaller, separately funded studies. In California, the CDPH TBCB is the primary CDC award recipient and coordinates TBESC activities.

The objective of Study #1, "Improving the Diagnosis and Treatment of Latent TB Infection," is to improve the diagnosis and treatment of LTBI. Activities in this study include evaluating: (1) Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRAs) in diagnosing LTBI and predicting progression from LTBI to TB disease; and (2) measures to enhance adherence to, and completion of, LTBI treatment. Successful completion of this project will provide valuable information needed to ensure widespread adoption of the best practice methods in California for preventing TB disease.

2. Service Location

Services shall be performed 1001 Potrero Avenue, Building 90, Ward 94 San Francisco, CA 94110, and travel as needed for complete deliverables.

3. Project Representative

A. Direct all inquiries to:

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies Task Order 1
Scope of Work

California Department of Public Health	Contractor
Fiscal: David Beers, Fiscal Analyst Tuberculosis Control Branch 850 Marina Bay Parkway Building P, 2nd Floor Richmond, CA 94804-6403 Telephone: (510) 620-3012 Fax: (510) 620-3030 E-mail: david.beers@cdph.ca.gov Study-related: Lisa Pascopella, PhD, MPH Project Director Tuberculosis Control Branch 850 Marina Bay Parkway Building P, 2nd Floor Richmond, CA 94804-6403 Telephone: (510) 620-3865 Fax: (510) 620-3030 E-mail: lisa.pascopella@cdph.ca.gov	L. Masae Kawamura, MD Site Principal Investigator San Francisco Department of Public Health TB Control Section 1001 Potrero Avenue Building 90, Ward 94 San Francisco, CA 94110 Telephone: (415) 206-8524 Fax: (415) 206-4565 E-mail: Masae.Kawamura@sfdph.org

B. Either party may make changes to the information above by giving written notice to the other party. Said changes shall not require an amendment to this agreement.

4. Services to be performed:

The Contractor will conduct an evaluation of the effectiveness of using tuberculin skin tests (TSTs) and Interferon Gamma Release Assays (IGRAs) in diagnosing latent tuberculosis infection (LTBI) and predicting the progression of LTBI to active TB disease. The contractor will work in collaboration with CDPH TBCB and CDC in obtaining Institutional Board (IRB) approval, developing a study protocol, performing a pilot study, evaluating the pilot study, revising the study protocol as needed and, conducting a full-scale study, per finalized protocol. In addition, the Contractor will perform protocol-required data entry and quality assurance activities, specimen collection, storage and shipment, data analysis, and collaborate on authorship for

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies Task Order 1
Scope of Work

publication of study results. The Site Principal Investigator, Epidemiologist I, and Research Nurse positions will perform the major functions, services and activities in this scope of work.

For additional details about the contractor's activities and responsibilities, please refer to the Scope of Work tables in Section 7 of this exhibit.

5. Subcontractor Requirements

No subcontracts may be used in performance of the scope of work.

6. Progress Reports or Meetings:

A. The Site Principal Investigator and/or designee shall attend meetings with CDPH TBCB, CDC, and other TBESC study site personnel to determine if contract performance is consistent with stated deliverables and timeframes, to provide communication of interim findings, and convey difficulties or special problems encountered so that remedies are quickly developed.

7. Detailed Description of the Services to be Performed:

BASE PERIOD: Five months (November 1, 2011 – March 28, 2012)

Goal: Participate in initial protocol development for Study #1, "Improving the Diagnosis and Treatment of Latent TB Infection"
Objectives: Finalize an initial study protocol for use in conducting a pilot study.

Major Functions, Service, and Activities	Responsible Party	Performance Measure and/or Deliverables
B.1 Review CDC-prepared draft protocol and participate in the development of an initial study protocol	Site Principal Investigator; Epidemiologist I	B.1.a Initial protocol will describe in detail the required procedures including laboratory tests (TST and IGRA), clinical and laboratory follow-up, monitoring patient adherence to treatment, reporting adverse treatment events, completion of LTBI therapy and follow-up to determine the number of study participants that progress from LTBI to active TB disease.

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies Task Order 1
Scope of Work

		B.1.b Complete review of CDC-prepared protocol and participate in scheduled meetings to provide feedback on feasibility and suggest improvements B.1.c Finalize study protocol and data collection forms

TASK PERIOD 1: Six months (March 29, 2012 – September 28, 2012)

Goal: Complete a pilot study with the intent of being able to initiate the full study beginning September 15, 2012.
Objectives: Obtain Institutional Review Board (IRB) approval, develop a study implementation plan, recruit and train study staff, conduct and evaluate a pilot study, and draft a final study protocol.

Major Functions, Service, and Activities	Responsible Party	Performance Measure and/or Deliverables
1.1 Obtain Institutional Review Board (IRB) approval through each study site and the State of California	Site Principal Investigator; Research Nurse	1.1.a Collaborate with CDPH TBCB and other California study sites to determine needed IRB approval 1.1 b Complete IRB approval requests and submit to respective IRBs
1.2 Develop step-by-step study implementation plan	Site Principal Investigator; Epidemiologist I; Research Nurse	1.2 a Participate in CDPH TBCB-scheduled meetings to develop a study implementation plan providing feedback on feasibility and appropriateness 1.2.a Develop plan and timeline for pilot study 1.2 c Present completed study implementation plan to CDPH TBCB for review 1.2.d Ensure laboratory capacity and performance requirements per study protocol
1.3 Recruit and train site remaining study staff	Site Principal Investigator; Research Nurse	1.3.a Develop job descriptions and duty statements for remaining study staff 1.3.b Complete hiring prior to pilot study 1.3.c Provide training for study staff on initial protocol requirements

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies Task Order 1
Scope of Work

1.4 Conduct pilot study	Site Principal Investigator; Epidemiologist I; Research Nurse	1.4.a Identify, recruit, enroll, screen, obtain participant consent, treat and follow per initial study protocol a minimum of 25 participants at high risk for LTBI or TB disease 1.4.b Enter and submit data into the CDC-developed data entry system using a password-protected entry system 1.4.c Report any adverse events per study protocol and in compliance with California and national requirements 1.4.d Ensure safe and timely shipment of initial protocol required participant specimens to designated laboratories or repositories 1.4.e Participate in scheduled monthly meetings providing feedback on pilot study progress, challenges and possible solutions
1.5 Evaluate pilot study and participate in drafting final study protocol	Site Principal Investigator; Epidemiologist I; Research Nurse	1.5.a Provide a summary of pilot study results 1.5.b Participate in scheduled meetings to provide feedback on pilot study results and suggest needed changes and/or improvements for final protocol 1.5.c Finalize all study forms

ACCEPTANCE OF AWARD

San Francisco Department of Public Health

San Francisco Department of Public Health, TB Control Section: Tuberculosis Epidemiologic Studies (TBESC) Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection"

FUNDING PERIOD: November 1, 2011 through September 23, 2012
AWARD: $23,538

I hereby accept this award. By accepting this award, I agree to the requirements as described in San Francisco Department of Public Health, Public Health Site Scope of Work, Budget, and the Policies and Procedures Manual for FY 2011-2012 and any other conditions stipulated by the California Department of Public Health, Tuberculosis Control Branch.

Authorized Signature

11/9/11
Date

Barbara A Garcia
Print Name

Director of Health
Title

INTRODUCTION FORM

By a member of the Board of Supervisors or the Mayor

Time Stamp or
Meeting Date

I hereby submit the following item for introduction:

- ☐ 1. For reference to Committee: _____
  An ordinance, resolution, motion, or charter amendment
- ☑ 2. Request for next printed agenda without reference to Committee
- ☐ 3. Request for Committee hearing on a subject matter
- ☐ 4. Request for letter beginning "Supervisor _____ inquires..."
- ☐ 5. City Attorney request
- ☐ 6. Call file from Committee
- ☐ 7. Budget Analyst request (attach written motion).
- ☐ 8. Substitute Legislation File Nos.
- ☐ 9. Request for Closed Session
- ☐ 10. Board to Sit as A Committee of the Whole
- ☐ 11. Question(s) submitted for Mayoral Appearance before the BOS on _____

Please check the appropriate boxes. The proposed legislation should be forwarded to the following:

- ☐ Small Business Commission
- ☐ Youth Commission
- ☐ Ethics Commission
- ☐ Planning Commission
- ☐ Building Inspection Commission

Note: For the Imperative Agenda (a resolution not on the printed agenda), use a different form.]

Sponsor(s): Mar

Subject: Resolution authorizing SFDPH to accept and expend retroactively a grant from SFDPH to participate in a program entitled "Tuberculosis Epidemiological Studies Task Order 1, "Improving the Diagnosis and Treatment of Latent Tuberculosis Infection."

The text is listed below or attached:

Please see attached.

Signature of Sponsoring Supervisor: _____

For Clerk's Use Only: