**Background and Project overview**

In 2013, approximately 9 million individuals developed TB disease globally, equivalent to 126 cases per 100,000 population.1 A key driver of TB transmission is the significant number of “missed” TB cases who are undiagnosed or experience significant delays in diagnosis and treatment.2-5 Such “missed” TB cases are likely to remain infectious for a lengthy period, and thereby contribute disproportionately to TB transmission.1 To stop the global epidemic of TB and decrease the number of missed cases of TB, The Global Plan to Stop TB 2016-20206 stresses, among other strategies, 1) early diagnosis of TB, including universal drug-susceptibility testing; 2) systematic screening of contacts and high risk groups; 3) rapid uptake of new interventions and strategies; and 4) research to promote innovations. **The overall goal of this proposal is to evaluate the utility of home-based point-of-care TB testing for early diagnosis and linkage to care of household contacts of TB patients, addressing the need for active case finding and early detection of infectious TB.**

Screening of household contacts (HHC) exposed to infectious TB patients is a fundamental component of TB programs and can lead to early diagnosis of new TB cases. The South African National Tuberculosis Management Guidelines state that contact investigations are a priority activity of the National TB Control Program (SA-NTCP).7 In 2011, South Africa introduced a nation-wide, multifaceted screening program focused on high-burden districts, which included household contact tracing, community mobilization, door-to-door screening in areas with a high burden of smear-positive TB cases, and screening of high-risk populations. This national campaign screened >150,000 HHC and identified >3000 new cases that would have otherwise not been detected through routine means.8 Despite the overall success of this program, there are significant barriers to conducting effective contact investigations. Our preliminary study of TB screening at health clinics identified TB infected individuals who self-reported being a household contact of a known TB patient, but who did not follow-up for TB testing at a clinic. This suggests that **the uptake of community-to-clinic referrals for testing is a major weakness of household contact investigations.** Likewise, a 2015 report of the country’s TB surveillance system found that 33.7% of all persons diagnosed with TB disease may not have been notified of their disease or initiated on treatment (‘initial defaulter’),9 suggesting that household contacts screened during contact investigations may be lost-to-follow up because of 1) their own health seeking behavior, and/or 2) they were never notified of their results.

In response to the urgent need for new, cost effective interventions and strategies to find and link-to-care missing cases of TB, we propose an exploratory study to 1) investigate the acceptability and feasibility of home-based TB testing of household contacts using a new portable GeneXpert point-of-care (PoC) platform with wireless linkage to a national TB database, and 2) determine the potential impact of such a home-based testing program on early detection of TB disease and linkage-to-care (LTC). *We hypothesize that among household contacts of TB patients, home-based point-of-care TB testing will increase early detection and linkage-to-care, and decrease time-to-treatment initiation of secondary TB cases compared to standard home-based TB symptom screening with referral for testing.*

**Economic costing overview**

As part of the costing component of the research study, FPD will evaluate the cost-effectiveness of the intervention. The aim of this component would be to determine the overall study implementation cost as well as the intervention’s scalability as a national programme. To achieve this, two separate costing models will be designed allowing for the estimation of project related costs as well as the cost of scaling for larger programme implementation.

The specific aims of the research project are to (1) determine the acceptability and feasibility of using point-of-care technology to perform home-based TB testing of household contacts of TB patients; and (2) to describe the outcomes of household contacts screened and tested for TB in their home compared to those screened and referred for testing in a health facility.

In conjunction with this research, the specific aims of the economic evaluation are to (1) measure the effectiveness of the two models of TB screening and testing; (2) calculate the costs of implementation and scale-up of both models; and (3) estimate the incremental cost-effectiveness in terms of cost per TB associated death and disability-adjusted life year (DALY) averted by implementation of home-based TB testing of household contacts through this intervention as compared to no implementation.

**Study location and description**

This study will recruit TB index patients from 6 health facilities that serve the Duncan Village Informal Settlement Area (DVIS) in Buffalo City Metro Health District (BCM), Eastern Cape Province, South Africa, and will be performed at households of TB patients. DVIS is a large township with a 2011 population census of 60,902 residents (population density of 27,071/sq mile; similar to New York City). In 2013, the TB incidence rate in BCM was 752/100,000, with an estimated incidence rate of 1509/100,000 in DVIS. During 2013, BCM had a 7.7% Rifampicin resistance rate amongst tested sputum specimens. Given the socio-economic characteristics of DVIS, TB indicators for residents of this area are likely far worse than for BCM overall.

In accordance with the South African National TB Management Guidelines (SA-NTMG), all smear positive TB (PTB) patients should be asked to provide a list of all household contacts for household contact investigations. For this study, clinic-based research assistants (RA-C) assigned to each of the 6 collaborating facilities will identify, recruit, and consent 1522 eligible individuals with PTB. Subsequent HCI appointments will be scheduled for each index patient. For HCI teams that successfully connect with individuals on the household contact (HHC) list, HCI teams will conduct TB symptom screening. In the intervention arm of the study, a total of 574 households with a symptomatic individual will be randomly selected to be offered a home-based GeneXpert® Omni MTB/RIF Ultra TB test. In the comparison group, 761 HHCs identified from the TB index patients will receive home-based TB screening with referral for TB testing in a health facility.

**Sampling strategy and data collection of time and motion**

The time and motion component of this costing analysis will utilize a convenience sampling strategy to capture data from work conducted during 3 phases of the study. In each phase, REDCap timing data and key-informant surveys will compliment and/or supplement observed data. The time and motion capture logs for each phase can be found in *Appendix L*. Specifically, these phases are (1) enrolment of index patients; (2) household contact investigations; and (3) presentation at the facility.

The time required to perform various intervention operations will vary between instances. For this reason, an effort will be made to take a large number of measurements in order for the results to be representative. The necessary sample size will be determined in the early stages of data collection. An initial pre-test sample of 5 time and motion observations will be collected. The standard deviation of pre-test time measurements can be used to calculate the necessary sample size at the 90% confidence interval that reflects a +/-2.5 min interval. Sample sizes will be calculated for each unique phase of the study separately.

Sample sizes will be calculated separately for each phase of the study, and in the case of household contact investigations, calculated separately for both the intervention and comparison arms of the study.

***Notes and limitations***: Given the innovative nature of this project, there is a high degree of uncertainty regarding the feasibility of successfully observing the preceding components. This necessitates the convenience sampling strategy and any subsequent changes that may be realized over the course of the study. For example, it may be found that the rate at which patients present to the clinics is much lower than expected. In this case, measurements for the time and motion component of this phase would rely on key-informant interviews (with nurse and/or RA-C) and REDCap data.

**Sampling strategy for capturing direct patient costs**

In addition to the time costs associated with the intervention, there is a societal cost in the opportunity cost in patients partaking in this study. For any point in which the patient is within the operational phases of the project, the patients time may be accounted for as equivalent to the measurements associated with the project. Additional costs will be accounted for through brief (4 question), voluntary surveys conducted on 24 patients. 12 surveys will be collected from individuals during the *enrollment of index patients* phase and 12 surveys will be collected from individuals during the *presentation at facility* phase. As surveys will focus on the patient’s travel time to the clinic, these surveys will not apply to the HHI phase. These surveys can be found in *Appendix K*.

**Methods**

*Costs*

Since FPD is adding an intervention component to the existing South African TB screening program introduced in 2011, the costing analysis will focus on incremental costs incurred as a result of the intervention of home-based Omni MTB/RIF Ultra TB testing.

This study proposes to collect data on the start-up activities and the direct program costs of establishing and operating an intervention for home-based PoC TB testing. The most important cost components for this study include personnel (operational planning, training workshops, contact time spent in reaching HHCs, monitoring and evaluation), supplies, equipment, promotion, and transportation. As this intervention works closely with on-going programs within the FPD Research Unit and the select health clinics operating within Duncan Village, Buffalo City Metro Health District, an effort will be made to estimate the indirect costs of resources (services and inputs) that are jointly used in the intervention.

This analysis will account for costing data through both expenditure and ingredient approaches. The expenditure approach utilizes budgetary and expense reports from FPD. As these reports are limited in their costing breakdown, the ingredient approach is a useful supplement. This ingredient approach will meticulously outline the quantities and prices of all inputs. For specific labor components, follow-up interviews, observations, and/or surveys will be used to estimate the amount of time personnel devoted to the project.

Some components of the time and motion study can be captured using the REDCap software. REDcap has the capacity to provide crude reports of the time each patient survey takes. Staff surveys and interviews will complement this data, offering insight as to what portions of services are applicable only to the research component of the study. For example, time-intensive components such as obtaining consent for research and communication with project managers can be accounted for in REDCap data following this supplemental data collection.

While certain budgetary components for this study are not relevant to the costing objective of providing data for scaling-up this intervention (i.e. international travel fees, research unit overhead), not all this information is omitted. This analysis will function as a comprehensive costing report of all research activities. Additionally, costs relevant only to components of the intervention that may be scaled up will be stratified out as well.

Table 1 summarizes the cost categories and expected data sources to be used in the study. When possible, a preliminary breakdown of costs specific to the intervention or FPD only have been made.

*Cost data collection: time and motion*

During the project implementation stage, we will conduct visits to oversee both the clinic and household contact components of the study. At the clinic level we will observe and/or speak to program managers, nurses, and RA-Cs. At the household level, we will observe and speak to the members of the HCI teams. Data at the clinic level will be entered directly into a template spreadsheet (one per clinic), and data for the household level will be entered accordingly. Costs for each of the six clinics will be assessed, with the number of assessments and time in which these assessments occur being representative of the projects as a whole. Time and monetary costs incurred by clients accessing the services offered by the intervention and the comparison group will be assessed through client interviews. A detailed breakdown of these time components can be found in *Appendix L*.

**Table 1: Cost categories and data sources**

|  |  |  |
| --- | --- | --- |
| **Data Type** | **Source** | **Collection Methods** |
| **Start-up Costs (*Intervention specific)***   * Project/program micro-planning * Hiring staff * Development of training materials * Development of project documents (Protocol, MOP, etc.) * Software development * Clinic arrangements and meetings * RA-C and RA-F recruiting advertisements | FPD budgets and GLs  Facility level data  Organization level data | Interviews with facility staff  Interviews with FPD staff  Budget expense reports  Project Expense reports |
| **Start-up Costs *(FPD specific)***  -Program development  -Software development | FPD budget and GLs  Organization level data | Interviews with FPD staff  Budget expense reports  Project expense reports |
| ***Contact Costs1* (*Intervention specific)***  -Salary grade/time of RA-Fs, RA-Cs, Nurses  *-*Salary grade/time of FPD staff | FPD budgets and GLs    Organization level data | Budget expense reports  Project Expense reports  Interviews with FPD staff  ***Appendixes A-I***  Time and motion observations  ***Appendix J-L*** |
| **Contact Costs (FPD specific)**  - -Salary grade/time of FPD staff | FPD budget and GLs  Organization level data | Interviews with FPD staff  Budget expense reports  Project expense reports |
| **Travel Costs (*Intervention specific)***  -Avis Car Rentals  -Petrol | FPD budgets and GLs    Facility level data | Budget expense reports  Project Expense reports  Facility level interviews |
| **Travel Costs *(FPD specific)***  -Accommodation  -Per Diem for key personnel  -Air travel (including return)  -Car rental | FPD budgets and GLS | Budget expense reports  Project Expense reports |
| **Supplies Costs(*Intervention specific)***  -Barcode stickers  -Medical Waste Containers  -Specialized backpacks  -sputum collection bottles NHLS  -Sputum collection tube 50 ml (Falcon)  -Sputum collection tube 15 ml (Falcon)  -Printing questionnaires  -General Printing and Stationary  - Airtime  - 3G  -OmniGene Sputum Transport Media  -PrimeStore Media  -Software licenses  -Consumables | FPD budgets and GLs | Budget expense reports  Project Expense reports |
| **Supplies Costs *(FPD specific)***  **-**Office supplies | FPD budgets and GLs | Budget expense reports  Project Expense reports |
| **Equipment Costs (*Intervention specific)***  -Tablets  -Cellphones and SIM cards  -Fingerprint scanners  -Voice recorders  -Fridge  -Barcode scanner  -Computer  -Filing cabinets  -GeneXpert® Omni MTB/RIF Ultra TB | FPD budgets and GLs | Budget expense reports  Project Expense reports |
| **Equipment Costs *(FPD specific)*** |  |  |
| **Training Costs (*Intervention specific)***  -Venue catering  -Stationary  \*FPD training time in Contact Costs | FPD budgets and GLs  Facility level data | Budget expense reports  Project Expense reports |
| **Training costs *(FPD specific)*** |  |  |
| **Other Direct Costs (*Intervention specific****)*  -Translation of questionnaires  -Fingerprint scanner registration  -Medical Waste Collection | FPD budgets and GLs  Facility level data | Interviews with FPD staff  Budget expense reports  Project Expense reports |
| **Other Direct Costs *(FPD specific)***  -Consultant Fees | FPD budgets and GLs  Facility level data | Budget expense reports  Project Expense reports |
| **Patients:**  Travel time  Financial burden (Transportation time, child care, and out-of-pocket expenses | Client interviews  Literature estimates | Surveys and key informant interviews  ***Appendix M*** |

|  |  |
| --- | --- |
|  | *Direct costs* |
|  | *FPD specific costs* |

1. Costs to reach target, recruitment, and carry out intervention

**Description of costs**

*Start-up costs*-this section will include program development costs. These include (but are not limited to) costs necessary to orchestrate efforts among the 6 participating facilities, and the costs associated with advertising and hiring the RA-C and RA-Fs. This will also include costs associated with training.

*Training*- this will include costs relevant to training the RA-Cs and RA-Fs that are directly involved in the enrollment of index patients and conducting house hold contact investigations (HHCI), respectively. Furthermore, facility nurses will receive minor training on the referral procedures of the study.

*Equipment Costs****-*** this section will include tablets, cellphones and SIM cards, fingerprint scanners, voice recorders, fridge barcode scanners, computers and filing cabinets, vehicles, GeneXpert® Omni MTB/RIF Ultra TB machine. In the case that equipment is shared with other programs, costs will reflect allocation of use to this study.

*Supplies*- this section will include supplies that are used at the facility for index patient enrollment and tracking (e.g. fingerprint scanners), and the supplies that are used during the HHCI. For HHC that are designated to the intervention group of the study, relevant supplies will include (but not limited to): barcode stickers, medical waste containers, specialized backpacks, sputum collection bottles, sputum collection tubes, printed questionnaires, OmniGene sputum transport media, sputum transport to MRC, PrimeStore Media, software licenses, and consumables.

*Travel costs*- This section will include the vehicle rental, vehicle purchases, and costs and the associated fuel costs.

*Contact Costs*- this section will include health worker time that is both directly (intervention specific) and indirectly (FPD specific) involved with this costing analysis. This will be done through defining the number of health workers involved in specified activities and obtaining an estimate of their time for each activity. Their time will be valued by obtaining information on their salaries and getting a common measure of cost per unit. Information on time allocation will be obtained primarily through interviews with staff to determine full time equivalent time that is used in each phase of the intervention. Alternatively, the survey software, Redcap, provides data on the time spent per survey. Such data will supplement the recall of the workers.

Expenditure reports will be obtained from project expense reports. In addition, data collection tools will be developed for capturing resources and costs incurred at various points of implementation.

**Additional potential costs to consider in costing the intervention:**

Other management of overhead costs from funding agencies at FPD and at the facility level.

**Measuring Impact**

The primary outcome of time-to-treatment initiation will be calculated as the number of days elapsed between date of HCI and date of clinic presentation. Comparisons will be conducted between 1) TB-infected household contacts tested in their home, and 2.) TB-infected household contacts tested in the clinic. Secondary outcome measures will include 1) rate of referral uptake, calculated as

***[number of household contacts presenting for clinical follow up/ total household contacts referred to clinical follow-up];***

2) time to presentation at the clinic, calculated as

**[*elapsed time between date of initial referral to date of presentation at the clinic];***

and 3) treatment initiation rate, calculated as

***[# household contacts diagnosed with TB and initiating treatment/ total household contacts diagnosed with TB].***

**Measuring cost effectiveness**

The cost effectiveness analysis will compare the incremental costs and benefits of the TB infected household contacts tested in their home compared to the status quo of household contacts tested in clinics. The primary outcome measure for the intervention is the effect of providing household contact with a referral-for-treatment, as compared to the standard referral-for-testing. The incremental cost effectiveness ratio (ICER) will, therefore, reflect the additional costs incurred through the intervention divided by the change in time before treatment.

The primary analysis will be conducted from the programmatic perspective (both intervention specific costs and with additional FPD costs).

This calculation uses the following methodology:

1. Numerator: Δ in costs of home-based TB testing intervention, including:
   1. Financial costs: The frontline intervention costs as described in *Costs* section
   2. Patient costs: The direct costs to patients from travel time and travel expenses
2. Denominator alternatives
3. Δ in days elapsed between HCI and clinic presentation
4. Δ in rate of referral uptake
5. Δ in time to presentation at the clinic
6. Δ in treatment initiation rate

*Sensitivity analysis and discount rates*

A sensitivity analysis will be performed to gain insight into cost drivers, and to determine how sensitive the cost-effectiveness results are to a significant but plausible variation in each of the most important cost parameters. This will allow for greater insight for considerations of scaling up this intervention beyond the scope of the project. Selection of these specific parameters will take into account data collection, thus will follow this phase of the study implementation. The range for other parameters can be designated at the outset of the costing project. For example, following the WHO Guide to Cost-Effectiveness Analysis, we will report all costs using a recommended discount rate of 3% per year, and an alternative 5% discount rate and undiscounted rate.

*Additional cost-effectiveness analysis*

A secondary analysis will be presented from the societal perspective, using economic productivity for TB disability averted and costs of accessing services. Following WHO guidelines, interventions may be considered cost-effective if the ICER is < 3 times local GDP and very cost-effective if the ICER is <1 times local GDP per DALY averted.

Using programmatic data from this project, we will estimate for- both the intervention and the control arm- the ICER per TB-associated deaths and DALY averted. Whenever possible, this dynamic transmission model will be parameterized to local data using study data and literature estimates.

**Timeline**

|  |  |  |  |
| --- | --- | --- | --- |
| **No** | **Activities** | **Expected Outputs** | **Timeline** |
| **1** | Finalize the economic evaluation protocol | Protocol developed | July 2018 |
| **1.1** | Finalize methodological approach | Methods described and approved | August 2018 |
| **1.2** | Modify interview guidelines or cost data questionnaires for both start up activities and on-going project activities | Guidelines and forms developed and/or revised | August 2018 |
| **2.** | Collection information form project reports and project expense reports on start-up activities and costs. | Start-up cost data collected from project expense reports and entered into excel spreadsheet files. | July 2018-August 2018 |
| **3.** | Collect information from project report, project expense reports and facilities on recurrent operational costs | Information on recurrent operational costs collected | September 2018 |
| **3.1** | Collect time and motion information from Clinics 1-6 | Data collected at facility level for *index patient* and *HHCs presenting at facility* phases | September 3, 2018- September 14, 2-18 |
| **3.1** | Collect time and motion information form HHCI phase | Data collected during HHCI | September 3, 2018- September 14, 2-18 |
| **4.0** | Follow up on missing or necessary supplementary data | Self-reported surveys from staff in East London (or if return trip possible, self-observed data) | October 2018 |
| **5.** | Enter cost data into excel | - | October-November 2018 |
| **6.** | Conduct cost data analysis | Summary costs using spreadsheet-based cost model | October-November 2018 |