**Objectives of the cost analysis**

The overall objectives of this costing component are:

* To construct and validate mathematical models to estimate the impact of pre-exposure prophylaxis (PrEP) on human immunodeficiency virus (HIV) transmission at population level in South Africa
* To assess the incremental costs of PrEP combined with adherence support interventions
* To estimate the cost-effectiveness and budget impact of targeted PrEP initiation and compare standard practice to the following three strategies for adherence support:
  + Through group-based community health clubs
  + Through individual-based one-on-one counseling
  + Through medication provision only (control arm)

**Study Location and Description**

This study will be conducted in King Williams town (rural site) and East London (urban site) in Buffalo City Municipality, Eastern Cape Province. Buffalo City Municipality has approximately 700,000 inhabitants. The general population HIV prevalence in the districts is 14% and antenatal HIV prevalence of 31.2%, above the national average of 29.7%[*SOURCE 2 IN PROTOCOL*]. The Foundation for Professional Development (FPD) implemented its Community-Based Counseling and Testing (CBCT) programme in the district; from October 2015-September 2016, FPD tested 49,911 individuals (68.5 per 1000 population) in Buffalo City Municipality.

FPD is currently monitoring 22 CBCT platforms located in 22 HIV high-burden sub-districts or local municipalities in South Africa. The CBCT program targets priority populations in the identified sub-districts through strategic mobilization efforts and targeted HIV testing and counselling (HTC) interventions. The programme achieves this by providing HIV testing services through mobile units, systematic door-to-door home-based, workplace, index patient training, key population (KP) outreach (a.k.a twilight) and the provision of self-testing kits. PrEP initiation nurses and research assistants will be integrated into these CBCT teams for the recruitment and enrollment of participants into the study.

The sample of enrolled participants may be divided into three sub-groups: *Immediate PrEP Acceptors, Early PrEP Acceptors, and Delayed PrEP acceptors.* Immediate PrEP Acceptors will enroll in the study immediately upon consenting to participation in the study. Early PrEP Acceptors will return within 14 days of initial offering and will be enrolled in the study following another confirmed negative HIV test. Delayed PrEP acceptors will return after 14 days and will be enrolled in the study following another confirmed negative HIV test, as well as a repeat of the baseline survey.

The study consists of two intervention arms, group-based Community Health Clubs (GCHCs) and Individual Adherence Support (IBAS), and a control arm consisting of passive adherence support. The study leverages extensively researched theory for improving medication adherence and incorporates these principles into both group and individual learning sessions. These learning sessions will provide participants with information about PrEP, define problems impacting adherence, generate alternative solutions, make decisions about the alternatives, and collaboratively decide on a plan regarding how to implement the solution.

The implementation for the main study is 36 months. Young women who enroll for the study are expected to remain in the study for 24 months from the date of enrollment.

**Measuring Costs**

This evaluation is intended to influence the delivery of such health services from the perspective of the Department of Health in South Africa, thus will incorporate costing information specific to scaling up the program nationally. This cost analysis will include the financial costs for all activities and inputs used to implement the study, as well as include an economic component that incorporates costs of resources that may have been either donated or shared with existing government health services that were leveraged in the implementation of this study. Overhead costs and expenses such as building infrastructure, maintenance, and building expenses will not be included in the cost analysis. This analysis will particularly focus on the value of all resources used to achieve the project outputs and health outcomes.

Activity-based costing will be used to identify the main activities, resources, and specific inputs used to support each main activity from all sources contributing to the intervention (project and government). Data collection will begin by listing all of the main activities associated with each component from the Manual of Procedures (MOP) and listing the specific resources and inputs used at different stages of implementation of the study.

This analysis will account for costing data through both expenditure and ingredient approaches. The expenditure approach utilizes budgetary and expense reports from implementing agencies. As these reports are limited in their costing breakdown, the ingredient approach is a useful supplement. The ingredient approach will meticulously outline the quantities and prices of all inputs. For specific labor components, follow-up interviews 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.

**Cost data collection and sampling strategy**

Time and motion data collection will be conducted during the group-based community health club and individual-based one-on-one counseling adherence support phases of the study. Additionally, all participants in comparison and intervention arms will receive some level of general adherence support at the onset of the study, thus time and motion data from this phase will be recorded as well. Six separate components will be considered for cost data collection. These components can be found in the following section.

The time and motion component of this costing analysis will utilize a convenience sampling strategy to capture data at various 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 to be developed).*

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 roughly ~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.

**Description of Costs**

***Start-up costs***: This section will include program development costs. These include (but are not limited to) costs necessary to mobilize efforts within the community, interviewing, hiring, and training of staff and advertisements.

***Materials and Supplies:*** This section will include computers and technological supplies, specimen collection and testing kits, medications, and printing, and refreshments (for participants taking part in the in-depth interview portion of the study). A more detailed breakdown of these costs can be found in TABLE 1.

**Travel Costs:**

*International Travel:* This section will include costs from each year of the project for research personnel to travel to project sites and to advise on study development and review progress. Costs will include international airfare, lodging, and taxi allowance.

*Local Travel:* This section will include the vehicle rental, vehicle purchases, and costs associated with fuel consumption.

***Contact Costs***: This section will include health worker time that is both directly and indirectly 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 time and motion studies conducted in the field. Secondary measures will include interviews with staff to determine full time equivalent time that is used in each phase of the intervention. Alternatively, the survey software, REDCap, has provides data on the time spent per unit/patient. Such data will supplement the recall of the workers as well as data from the time and motion studies.

***Training Costs*:** This section will include project-specific training that will be provided to the team members working on the project at project initialization and whenever a need arises. These costs include rental of venues, light catering for the training events, and printing materials. The *Contact Costs* for research staff salary grade/time is not counted in this section.

***Other Direct Costs*:** This section will include a range of miscellaneous costs that may be incurred during startup, the intervention, or both. These costs include participant reimbursements, ADP/ computer services, office rental and renovations, translation and transcription, specimen transport, and report writing and dissemination.

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.

**TABLE 1**

|  |  |  |
| --- | --- | --- |
| **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 * Hiring advertisements * PrEP awareness advertisement campaign | FPD budgets and General Legers (GL)  Facility level data  Organization level data | Interviews with facility staff  Interviews with FPD staff  Budget expense reports  Project Expense reports |
| **Start-up Costs *(Research 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 PrEP Initiation Nurses  - Salary grade/time of PrEP Initiation Research Assistants  - Salary grade/time adherence support nurses  - Salary grade/time adherence support counselors  *-*Salary grade/time of FPD staff | FPD budgets and GLs    Organization level data | Budget expense reports  Project Expense reports  Interviews with FPD staff  Time and motion observations |
| **Contact Costs (*Research 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)***  -Car Rentals  -Petrol | FPD budgets and GLs    Facility level data | Budget expense reports  Project Expense reports  Facility level interviews |
| **Travel Costs *(Research Specific)***  -Accommodation  -Per Diem for key personnel  -Air travel (including return)  -Taxi fare | FPD budgets and GLS | Budget expense reports  Project Expense reports |
| **Materials & Supplies Costs (*Intervention specific)***  -Computer tablets  -Voice recorders  -Fingerprint scanners  -Handheld barcode scanners  -Earphones  -Specialized backpacks  -Qualitative analysis software  -Filing cabinets  -HIV test kits  -Pregnancy test kits  -STI testing kits  -Creatine Clearance Testing (CrCL) testing kits  -Medications  -Printing of questionnaires, project materials | FPD budgets and GLs | Budget expense reports  Project Expense reports |
| **Supplies Costs *(Research Specific)***  **-**Office supplies  -Printing of office supplies | FPD budgets and GLs | Budget expense reports  Project Expense reports |
| **Training Costs (*Intervention specific)***  -Venue rental  -Venue catering  -stationary and printing  \*FPD training time in Contact Costs | FPD budgets and GLs  Facility level data | Budget expense reports  Project Expense reports |
| **Training costs *(Research Specific)*** |  |  |
| **Other Direct Costs (*Intervention Specific****)*  -Participant reimbursement vouchers  -ADP/ Computer services (Airtime and 3G for staff cell phones)  -Office rental and renovations (including furniture)  -Translation of participant questionnaires  -Transcription of recorded interviews and focus groups  -Specimen Transport  -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 *(Research 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 |

**Measuring Impact:**

The outcome measurement of the project is the number of infections averted among adolescent girls and young women (AGYW) through the program interventions: the difference in the number of infections that occurred with cognitive behavioural-based adherence support programs and the number of infections that would have occurred without cognitive behavioural-based adherence support programs. The benefits of the intervention are expected to come through an increase in adherence due to two independent support platforms, which are:

1) group-based community health clubs adherence program and

2) Individualised adherence support activities.

The estimated infections averted will be based on a number of assumptions regarding project coverage and uptake of PrEP service in the care cascade system. A counterfactual simulation will be developed to predict the expected number of HIV seroconversions in Rea Phela 002. The results will be compared to the observed HIV incidence over 24 months. We will also evaluate the impact on HIV incidence in the overall population (male and female) and the possible combinations of cost effective intervention components that are sufficient to achieve a predefined percentage (for example 20%, 30%) reduction of population level HIV incidence over 5 and 10 years. The measurement of intervention effectiveness (adherence) will be conducted on Dried Blood Spots (DBS) collected directly from participants on a monthly basis starting on the first month after PrEP initiation.

***Estimating incidence rate without intervention (control arm):***

This highlights the low adherence support to PrEP medication where participants will only receive brochures and information booklets at enrollment and some adherence support two weeks after enrollment. Participants will be reminded to collect their monthly medication refills. This is the baseline scenario. Historical coverage levels for PrEP is not yet available in South Africa. For modelling purposes different coverage will be explored in the simulations.

Calculations for HIV Cost-effectiveness will be based on the basic guide provided by the Centres for Disease Control and Prevention (CDC) division of HIV/AIDS Prevention. Participants are expected to remain in the study for 24 months. However, in reality some participants may be lost during follow-up for a variety of reasons. Calculations used in this study will account for varying time periods of follow up which may occur in real life settings.

*New infections is the total number of new HIV cases in the given time period.*

*Total person-time at risk during the study = sum of each participant time at risk in the given time period*

*Incidence rate = #of new HIV cases in a given time period/Total person-time at risk during the study*

*PrEP Cost = Baseline cost of the drug without/with minimal adherence intervention costs*

***Estimating incidence rate with intervention (Group-based Community Health Clubs (GBHC)):***

This will incorporate GBHCs facilitated by trained Lay Health Counsellors (LHC). LHCs will be young women preferably with prior PrEP experience. The LHCs will have access to PrEP for the duration of the study if they desire. Each GBHC will consist of a maximum of 20. Multiple GBHC’s sessions will be held at secure, safe and centrally located area within the study community. Monitoring of sessions will be done to ensure that the intervention is implemented as per protocol. To facilitate communication participants will join a WhatsApp group.

The number of infections with the intervention will use a mix of results in the data from the study and modeling. We will use CDC cost-effectiveness analysis of prevention interventions for HIV guide to estimate the impact of the intervention. Incidence rate calculation will be the same as the calculation without intervention. The effect of GBHC will be measured by the difference in the incidence rate in AGYW who receive PrEP with GBHC adherence support and the incidence rate of AGYW who received PrEP without adherence support (baseline scenario).

*Incidence rate = #of new HIV cases in a given time period/Total person-time at risk during the study*

*Total cost of PrEP =#of PrEP participants \* Cost of administering PrEP with adherence support*

*Cost effectiveness = Annual or monthly program cost/Annual or monthly #of new HIV cases*

*Model calculations:*

*Infections averted = Baseline new infections – GBHC intervention new infections*

*PrEP cost per infection averted = Total cost of PrEP/ Infections averted*

***Estimating incidence rate with intervention (Individualised Adherence Support (IAS)):***

Each IAS participant will be matched to a LHC for theduration of the study. Individualised adherence sessions which allow participant-driven discussion will be scheduled once a month. The number of infections with the intervention will use a mix of results in the data from the study and modeling. Cost-effectiveness analysis and Incidence rate calculation will be the same as the calculation with intervention (GBHC). The effect of IAS will be measured by

1. The difference in the incidence rate in AGYW who receive PrEP with IAS adherence support and the incidence rate of AGYW who received PrEP without adherence support (baseline scenario).
2. The difference in the incidence rate in AGYW who receive PrEP with IAS adherence support and the incidence rate of AGYW who received PrEP with GBHC adherence support

*Incidence rate = #of new HIV cases in a given time period/Total person-time at risk during the study*

*Total cost of PrEP =#of PrEP participants \* Cost of administering PrEP with adherence support*

*Cost effectiveness = Annual or monthly program cost/Annual or monthly #of new HIV cases*

*Model calculations:*

*Infections averted = Baseline new infections – IAS intervention new infections*

*PrEP cost per infection averted = Total cost of PrEP/ Infections averted*

**Cost analysis**

Data will be entered and analyzed in Excel to provide the total incremental costs of each intervention.

**Measuring program impact**

The goal of the program is to avert HIV infections through both increased PrEP initiation and adherence. This costing analysis will focus on the incremental costs incurred as a result of each intervention, beginning with the Community-Based Counseling and Testing and culminating at the primary endpoints outlined in the main study protocol. These endpoints will test for PrEP adherence using tenofovir diphosphate (TFV-DP) levels assessed among arms and compared at 3, 6, 12, 18, and 24 months.

Modeling of these program results will help to depict the difference in estimated number of HIV infections that would occur without the intervention, and/or that would occur with each unique arm of the intervention.

**Measuring cost effectiveness**

The cost effectiveness analysis will compare the incremental costs and benefits of the intervention compared to the status quo of current HTC capacities in South Africa. The incremental cost effectiveness ratio (ICER) will be measured by the additional costs incurred through the intervention divided by the additional number of infections averted through the intervention (compared to the number of infections averted through no intervention).

This cost analysis will also provide information on the cost per young woman initiated on PrEP, the cost per young woman adhering to PrEP treatment at the 3, 6, 12, 18, and 24-month endpoints. Finally, we will provide information on the cost profiles of total costs by cost category.

**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 | July-September2018 |
| **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-September 2018 |
| **3.** | Collect information from project report, project expense reports and facilities on recurrent operational costs | Information on recurrent operational costs collected | October 2018 |
| **3.1** | Collect time and motion information on PrEP initiation from each of the 4 HTC modes | Data collected at HTC phase | October  2018 |
| **3.1** | Collect time and motion information on PrEP adherence from each adherence support mode | Data collected at adherence support phase | October 2018 |
| **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) | November 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 |