Analysis Plan for the Cost-effectiveness of the HPTN 071 (PopART) Intervention in Zambia and South Africa

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Version 1.0

14 December 14, 2018

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1. Introduction

Cost-effectiveness analyses (CEAs) estimate the costs and health gains of alternative interventions. They provide a method for prioritizing the allocation of resources to health interventions by identifying the interventions that have the potential to yield the greatest improvement in health for the available budget. CEAs quantify the effects or gains in population health as a result of a particular policy or intervention. The gains are measured in physical units (cost-effectiveness analysis), or a generic measure of health (cost-utility analysis) such as disability-adjusted life years (DALYs), representing a weighted combination of mortality and morbidity effects of an intervention. CEAs furthermore provide for the quantification of the net costs of the intervention, and an assessment of those costs per unit of health gained, such as cost-per infection averted. The cost-effectiveness of a therapeutic or preventive intervention is the ratio of the incremental cost of the intervention to a relevant measure of its incremental effect.

This document explains the economic analysis plan of the cost-effectiveness of the HPTN071 (PopART) intervention compared to standard of care in Zambia and South Africa. The cost-effectiveness of the HPTN071 (PopART) intervention package is analysed by combining economic data and the predictions of the epidemiological model, most importantly the key outcome 'infections averted'. The primary economic analysis will focus on the costs and cost-effectiveness of the components of the HPTN 071 interventions specified by the epidemiological model - in the Arm A study communities of the HPTN071 (PopART) trial compared to a situation without the HPTN071 (PopART) intervention in these communities. Separate CEAs can be conducted on alternative scenarios regarding national roll-out of the intervention in the countries, different counterfactual scenarios including improved testing and treatment from health facility investments in the comparator arm and on selected alternate intervention packages.

2. Primary Research Question

The primary research question of the economic analysis is whether the HPTN071 (PopART) intervention is cost-effective compared to a counterfactual of standard of care in Zambia and South Africa. The objectives of the economic evaluation of HPTN071 (PopART) as specified in the trial protocol are:

- Measure the incremental cost of the two intervention packages through systematic recording of costs in intervention and control communities.
- Estimate the effectiveness and cost-effectiveness of the intervention packages and alternative packages, both in the chosen study populations and in other populations by fitting mathematical models based on the empirical data from the trial, including data related to cost.
- Measure the burden experienced by local health centres due to implementation of the intervention in the community

3. Scenarios modelled, Analysis Perspective and Time Horizon

The CEA can estimate the cost-effectiveness of a range of scenarios concerning roll-out of the intervention, and alternative approaches on how benefits and costs are calculated. Here is an exhaustive list of possible scenarios and approaches, for discussion and review. All of these scenarios and approaches have their pros and cons, and not all of them will be actually estimated and included in the final report and published:

(1) **Interventions discontinued:** The CHiPs interventions are discontinued at the end of the trial, from which time onwards HIV testing and treatment are provided according to standard of care in the two countries. The IBM projects outcomes until 2030. The CEA can adopt two approaches:
   a. Benefits (infections and DALYs averted) and costs are estimated until 2030, from which point onwards no further benefits and costs are counted ('world end');
   b. DALYs averted and costs are estimated until 2030, from which point onwards DALYs averted are calculated based on the remaining life expectancy of all individuals who are alive in 2030 ('closed cohort').

(2) **Interventions continued:** The CHiPs interventions are continued after the end of the trial, and the IBM projects outcomes until 2030 and until 2050 in an alternative scenario. The CEA can adopt two approaches:
   a. Benefits (infections and DALYs averted) and costs are estimated until 2030 (or 2050), from which point onwards no further benefits and costs are counted ('world end');
   b. DALYs averted and costs are estimated until 2030, from which point onwards DALYs averted are calculated based on the remaining life expectancy of all individuals who are alive in 2030 ('closed cohort'). There is no 'closed cohort' approach for the 2050 projection scenario.

At a later stage, the efficacy and cost-effectiveness of alternative scenarios on national roll-out can be estimated:

(3) **HPTN071 (PopART) 'light':** The CHiPs interventions are delivered until the end of the trial; after then, the intervention is modified. For example, the frequency of testing round is decreased, a reduced package of services is delivered, the interventions are targeted towards high prevalence communities, or targeted at specified subgroups of the population. The IBM projects outcomes until 2030 and until 2050. The CEA can adopt two approaches:
   a. Benefits (infections and DALYs averted) and costs are estimated until 2030 (2050), from which point onwards no further benefits and costs are counted ('world end');
   b. DALYs averted and costs are estimated until 2030, from which point onwards DALYs averted are calculated based on the remaining life expectancy of all individuals who are alive in 2030 ('closed cohort'). There is no 'closed cohort' approach for the 2050 projection scenario.

The CEAs are conducted from a health system perspective. Benefits and costs are discounted at 3.5% and converted into their net present value for all scenarios and approaches. For all scenarios, the modelled estimates of outcomes for the HPTN071 (PopART) interventions are compared against the modelled estimates of outcomes for enhanced standard-of-care in arm C communities (counterfactual). Actual trial data are used to calibrate the IBM and generate projections for both intervention and counterfactual. The counterfactual reflects guideline changes on ART initiation that occurred during the trial in both countries. Changes in the underlying trend of testing and treatment initiation are incorporated into the IBM and the CEA, via changes in the number of individuals in different categories.

4. Outcomes of the Analysis

The primary outcome for the cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER) of cost per infection averted, analogous to the primary outcome of the trial - infections averted. In addition, cost-utility analysis will use disability-adjusted life years (DALYs) as the outcome, reporting results as cost per DALY averted.

In reporting the findings, the economic analysis will disaggregate cost projections into annual costs of home-based testing and counselling by Community HIV Care Providers (CHiPs), costs of ART, costs of CD4 and HIV testing in health facilities; variations in estimates of benefits and costs across communities will also be reported (Figures 1 to 4).

5. Effectiveness

The effectiveness estimates of infections averted used by the economic analysis are generated by the epidemiological individual based model (IBM). The main output generated by the IBM is infections averted per year. Infections averted will then be translated into DALYs averted by considering the average remaining life-expectancy of individuals according to age group and gender in the country.

The HPTN071 (PopART) individual-based model (IBM) is a computer simulation model of the HIV epidemic in the HPTN071 (PopART) communities. It models a simulated population of approximately the same size as each HPTN071 (PopART) community. The model uses data from the trial, the UN Population Division on mortality and fertility within Zambia and South Africa, and others, introduces HIV into the simulated population between 1970-80, models partnership formation and dissolution, HIV progression, and both the HPTN071 (PopART) intervention and a background care cascade.

HIV transmission is assumed to occur between heterosexual couples. Partnership formation and dissolution is informed using data from the baseline Population Cohort. Three risk groups, allowing different numbers of concurrent partners and duration of partnerships, are modelled. HIV disease progression is assumed to follow data from the AIDS Therapy Evaluation in the Netherlands (ATHENA). The IBM models both the HPTN071 (PopART) intervention and a background care cascade. Within arm A communities, CHiPs teams are

assumed to visit individuals within each community with a coverage, stratified by age and sex, that matches data from the field. HIV testing, with assumed 100% sensitivity and specificity, is carried out with each simulated CHiPs visit, and individuals with an HIV+ test result are offered ART immediately within simulated arm A communities. Time until ART initiation following an HIV+ test result is modelled following data from the trial.

Individuals starting ART can either become virally suppressed, virally unsuppressed, or dropout of care at a later date, and risk of HIV transmission to partners is dependent upon an individual's profile within the care cascade. The simulated background care cascade differs from the HPTN071 (PopART) intervention in ART eligibility, and dropout rates. Repeat CD4 testing (for those not eligible for ART immediately) is simulated in the background care cascade. Voluntary medical male circumcision (VMMC) is offered to any HIV negative male following a negative HIV test and VMMC uptake is assumed to be different between HPTN071 (PopART) and the background care cascade. VMMC is assumed to offer a 60% reduction in susceptibility and traditional male circumcision is assumed to offer no protection. Circumcision coverage, both VMMC and TMC, differs by country according to population cohort data.

The model is calibrated using two main data sources: 1) data on prevalence and the first two 90's from the CHiPs intervention of the HPTN071 (PopART) trial and 2) prevalence from historical surveys from each country. Both of these sources of data are stratified by age and gender. The CHiPs intervention for rounds 1-3 provide estimates of a) prevalence, b) proportion aware of status of those HIV+, and c) proportion on ART of those aware of status. Historical data from surveys published by Demographics and Health Survey (DHS) in Zambia and the Human Sciences Research Council (HSRC) of South Africa. Regional prevalence estimates, stratified by age and gender, are provided in 2002, 2007, and 2013 by the DHS for Zambia, and in years 2002, 2005, 2008, and 2012 by the HSRC in South Africa. The model also uses data from the baseline population cohort to estimate parameters associated with partnership formation and different levels of risk of sexual behaviour.

Parameterization of the model involves generating a large range of candidate parameter sets and simulating an epidemic using each parameter set to determine the level of concordance between the data outlined above and the simulated analogues of this data. Those parameter sets that produce simulation results with the highest concordance with the data are kept. Model output for the cost-effectiveness analysis uses a single best fitting parameter set generated using this approach. IBM output for the selected parameter set will include model stochasticity captured through 40 model runs. To each of these 40 runs, the best estimate of costs is attached. Population numbers in the IBM reflect the population sizes in each trial community, estimated in 2013.

6. Costs

6.1. Intervention Costs

Intervention costs of home-based testing and counselling (HBTC) for HIV through CHiPs are captured as the unit cost per person tested and counselled at home. The unit cost is calculated as the time spent to deliver this specific component of the intervention multiplied by the per minute cost of a team of CHiPs, to which the costs of HIV test kits and consumables, the cost of equipment for each CHiP, CHiPs administrative and travel costs, and HPTN071 (PopART) administrative overheads are added. Some components of the HPTN071 (PopART) intervention are not included in the IBM, and therefore not in the economic analysis. For example, screening for TB and STIs.

6.1.1. Time spent to deliver the HPTN071 (PopART) Interventions

A time-and-motion (TAM) study was conducted in both countries in 2018. In the study, randomly selected teams of CHiPs were shadowed over 2 days to observe the time in minutes spent on specific activities and tasks. In total 32-person days of data were collected across the 12 trial communities. This data are used to calculate the time (in minutes) it takes to deliver home based testing and counselling (HBTC) to one individual seen by a team of CHiPs.

Table *1* lists the CHiPs activities included. The time spent distinguishes between individuals with the following test result: HIV-positive newly diagnosed and HIV-negative individuals. The IBM provides estimates for the number of individuals in each of these categories per year, therefore separate cost estimates are generated for these categories by applying findings from the TAM on the time invested for category of individual.

6.1.2. Personnel and Equipment Costs

Personnel costs (salaries including benefits) for the CHiPs and the intervention management cadre are taken from human resource data and from financial status reports and converted to per minute cost of providing HBTC. CHiP equipment costs are also be taken from study data and include a range of items including electronic data capture devices, rucksacks, bags, clothes etc. Cost of HIV test kits include the cost of Determine test kits and the additional cost of UniGold confirmatory test kits for those testing HIV-positive, costs of supply chain and supplies for conducting HIV tests. Administrative overheads and travel costs for CHiPs are allocated to each person covered by the interventions (regardless of type of client) and added to the per person costs.

6.2. Health Facility Costs

See

Table 3 for other cost parameters. These include the unit cost of HIV and CD4 testing in health facilities; cost per person per year on anti-retroviral treatment from the facility survey conducted under HPTN071 (PopART), and where there are gaps, secondary data is used to replace estimates of costs; unit cost of voluntary medical male circumcision (VMMC), the annual cost of health care treatment for individuals not on treatment by CD4 stage and the annual cost of end-of-life care.

7. Cost-effectiveness Analysis

The primary economic analysis will estimate the incremental cost-effectiveness ratio (ICER) of the provision of UTT in Arm A communities in the trial with the counterfactual of standard of care. The point estimate of the incremental cost-effectiveness ratio (ICER) are generated using the best parameter set from the IBM. This will include 40 stochastic model runs for this parameter set. To each of these 40 runs, the best estimate of costs is attached to generate the base-case ICER. Average costs and average infections averted across the 40 model runs for treatment and comparator are used to compute the base-case ICER as following:

$$ICER = \frac{\sum_{i=1}^{n} \bar{C}_{Ai} - \sum_{i=1}^{n} \bar{C}_{Ci}}{\sum_{i=1}^{n} \bar{E}_{Ai} - \sum_{i=1}^{n} \bar{E}_{Ci}}$$

Where *i* represents the trial arm A communities and *n=4* in Zambia and *n=3* in South Africa; $\bar{C}_{Ai}$ and $\bar{C}_{Ci}$ are the arithmetic mean costs in each community *i* averaged over the stochastic realisations of the IBM in the intervention and comparator arm respectively. $\bar{E}_{Ai}$ and $\bar{E}_{Ci}$ are the arithmetic mean infections averted in each community *i* averaged over the 40 stochastic realisations of the IBM in the intervention and comparator arm respectively. Cost–utility analysis are conducted in a similar manner as the cost-effectiveness analysis with DALYs being the measure of health benefit.

7.1. Probabilistic Sensitivity Analysis

To incorporate uncertainty in cost parameters, probabilistic sensitivity analyses are used. This involves random draws (upto 10,000) from specified cost distributions (See

Table 3 for specified distributions). For each draw, the incremental cost and effectiveness are calculated. The mean ICER across these simulations are estimated and compared to the base-case ICER.

$$ICER = \frac{\sum_{i=1}^{n} \bar{\bar{C}}_{Ai} - \sum_{i=1}^{n} \bar{\bar{C}}_{Ci}}{\sum_{i=1}^{n} \bar{E}_{Ai} - \sum_{i=1}^{n} \bar{E}_{Ci}}$$

Where *i* represents the trial arm A communities and *n=4* in Zambia and *n=3* in South Africa; $\bar{\bar{C}}_{Ai}$ and $\bar{\bar{C}}_{Ci}$ are the arithmetic mean costs in each community *i* averaged over the 10,000 cost parameter draws in the intervention and comparator arm respectively.$\bar{E}_{Ai}$ and $\bar{E}_{Ci}$ are the arithmetic mean infections averted in each community *i* averaged over the 40 stochastic realisations of the IBM in the intervention and comparator arm respectively.

In addition, sensitivity analyses are conducted on parametric uncertainty in the IBM, by replicating the probabilistic sensitivity analysis over multiple IBM parameter sets to evaluate robustness of the base-case cost-effectiveness results.

7.2. Presentation of Results

Uncertainty around the costs and effects are presented using incremental cost-effectiveness planes. The cost-effectiveness plane (Figures 5 and 6) visually represents the differences in costs and health outcomes between HPTN071 (PopART) and standard of care in two dimensions, by plotting the costs against effects on a graph. Cost-effectiveness planes show the uncertainty around cost-effectiveness outcomes, presented as a cloud of points on the plane corresponding to different iterations of the economic model in the probabilistic sensitivity analysis.

To evaluate decision uncertainty, cost-effectiveness acceptability curves (CEAC) are presented (Figure 7). The cost-effectiveness acceptability curve (CEAC) is a graph summarising the impact of uncertainty on the result of an economic evaluation, expressed as an ICER in relation to possible values of the cost-effectiveness threshold. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention is cost-effective at that threshold on the vertical axis. It helps the decision-maker evaluate the probability of the HPTN071 (HPTN071 (PopART)) intervention being more cost-effective than standard of care at any given threshold level for the ICER.

8. Table Shells

Table 1: CHiP activities from time and motion study

Activity	**Time spent (minutes) per client South Africa/Zambia**
CHiP offers the intervention	
CHiP explains the purpose of the visit	
CHiP offers available options of HIV testing (finger prick/self-testing)	
CHiP conducts pre-counselling for finger prick procedures	
CHiP conducts HIV finger prick test	
HIV testing Other	
CHiP gives HIV results, conducts counselling HIV positive client	
For those HIV-positive CHiP conducts confirmatory test	
CHiP gives HIV results, conducts counselling HIV negative client	
CHiP conducts counselling, refers to care and encourages adherence (HIV+ client already aware of status)	
CHiP promotes PMTCT (HIV+ pregnant women)	
Post test other	
CHiP conducts TB screening	
CHiP collects Sputa for TB testing	
CHIP conducts STI screening	
CHiP distributes and demonstrates condoms	
TB & STI screening etc Other	
CHiP enters data in EDC either a	
CHIP takes sputa to laboratory for TB testing (at clinic)	
CHiP writes referral letters	
CHiP follows up with health facility on HIV positive client	
CHiP follows up with health facility on TB patients	
CHIP follows up on STI patients	
CHIP follows up on PMTCT clients	
CHIP follows up on VMMC clients	
Linkage to care Other	
Administration, training and communication (time per client seen)	
Work related travel (time per client seen)	

Table 2: Parameter input data for individual based model

Table 3: Cost parameters and corresponding distributions for probabilistic sensitivity analysis

Cost component	**Base case value South Africa/Zambia**	**PSA Distribution**	**PSA parameters South Africa/Zambia**	**Source**
Intervention costs				
Time spent on HIV testing and counselling per client		Uniform distribution for time spent per HIV test		HPTN071 (PopART) programme data, time and motion study
Per minute cost of two personnel for home-based testing		Gamma		HPTN071 (PopART) programme data
Unit cost of Determine HIV test kits		Known point estimate		Programme data and Mwenge et al (2017 - Plos One)
Unit cost of UniGold HIV test kits		Known point estimate		Programme data and Mwenge et al (2017 - Plos One
Cost of CHiP equipment per person covered		Known point estimate		Programme data
Cost per person tested				Based on above Cost per person tested = time spent on HIV testing and counselling * per minute cost of personnel + Unit cost of HIV test kits+consumables + equipment
Facility Costs				
Cost per person tested in the facility		Gamma		Facility survey, Mwenge et al 2017 – Plos One Bautista-Arredondo et al 2016
Unit cost of CD4 testing		Gamma		Cassim et al 2014
Cost per person per year on ART		Gamma		Facility survey, Programme data /MATCH Study, Plos One 2016
Unit cost of a VMMC		Gamma		Vandement et al 2016 Tchuenche et al Plos One 2016

Annual health care cost per HIV-positive person not on ART CD4>350		Known point estimate		Eaton et al LGH 2014
Annual health care cost per HIV-positive person not on ART CD4200-350		Known point estimate		Eaton et al LGH 2014
Annual health care cost per HIV-positive person not on ART CD4<200		Known point estimate		Eaton et al LGH 2014
Annual per person cost of end-of -life care		Known point estimate		Eaton et al LGH 2014

Table 4: Results of the cost-effectiveness analysis

Variable	**Infections**	**Costs**	**ICER ($ per infection averted)**	**DALY ($ per DALY averted)**
South Africa				
Standard of care				
UTT				
Zambia				
Standard of care				
UTT				

9. List of Figures