Integrating Paediatric TB services into child healthcare services in Africa (INPUT) - A cluster-randomized stepped wedge trial

HEALTH ECONOMICS ANALYSIS PLAN (HEAP) VERSION 1.0 (//)

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Section 1: Administrative Information 1.1 HEAP Administrative Information

Integrating Paediatric TB services into child healthcare services in Africa (INPUT) - A cluster-randomized stepped wedge trial
NCT03862261, ClinicalTrials.gov
Elizabeth Glaser Paediatric AIDS Foundation
The purpose of this HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan and it should be read in conjunction with them.
This document has been written based on information contained in the trial protocol version 2.0, dated 11/06/2019
SAP Version 1.0, 02/07/2018
HEAP Version 1.0, 31/01/2020
This HEAP was prepared by Dr Nyasha Mafirakureva (health economist), Dr Pete Dodd (mathematical modeller) and Prof Simon Dixon (senior health economist) and approved by the PWC*. The trial health economist(s) [Dr Nyasha Mafirakureva, Dr Pete Dodd and Prof Simon Dixon] are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

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Section 2: Trial Introduction & Background

2.1 Trial Background and Rationale

The burden of paediatric TB is substantial with the World Health Organization (WHO) estimating that, in 2017, about one million children (under 15 years) were affected by TB worldwide, and more than 235,000 children died due to this disease, including 40,000 HIV/TB co-infected children[1]. Sub-Saharan Africa accounts for about one-third of all paediatric TB cases with an incidence of 29-34/100,000, which is double the global average [2]. In HIV-endemic African countries, 40-60% of paediatric TB patients are also infected with HIV[3].

TB in children is largely under-diagnosed due to non-specific symptoms and difficulties in obtaining specimens for diagnosis[4] making it hard to assess the actual burden of the childhood TB epidemic[5]. As a result, only 39% of estimated paediatric TB cases are notified to national TB programs (NTPs), leaving a large proportion of children undiagnosed or unreported[1]. Furthermore, the treatment of children with active TB is largely centralized and is provided as vertical services in many sub-Saharan African countries[4, 6]. This represent another barrier to identification of cases and scale up of treatment of children with TB further compounding under-diagnosis and under-reporting. Weak case finding, lack of and underuse of diagnostic tools, inadequate linkage to care, and lack of appropriate paediatric TB formulations result in poor clinical outcomes [4, 7].

Until recently, TB medicines did not exist in formulations that were appropriate or well-tolerated by children[8]. Additionally, effective preventive therapy is now available to help ensure children exposed to TB do not develop TB disease[9]. However due to several barriers to access for TB services these treatments are not being widely used[10, 11]. Improving access to TB screening and diagnosis, TB medications and preventive therapy could reduce the global burden of paediatric TB. Innovative approaches that focus on integration and decentralization of paediatric TB services are required to broaden access to diagnosis, care and treatment among children in need. Integration of care into existing health services is one approach that has had success in HIV/AIDS care where evidence shows it is feasible, does not compromise care and improves retention in care[12, 13]. Although there is growing evidence demonstrating that integrating TB services into HIV services results in good quality care and improved retention in adults, very limited data are available on the integration of TB care, and treatment outcomes[14, 15].

Generating evidence on the feasibility and impact of innovative approaches to integrating paediatric TB services into existing child health services could improve access and reduce the burden of paediatric TB. Additionally, evidence on the costs and cost-effectiveness of these approaches will inform policy and aid decision-making. Our objective is to perform an economic evaluation alongside a multinational stepped wedge cluster-randomized intervention study assessing the impact of integrating TB screening and diagnosis in children under 5 years of age into child healthcare services in comparison to the standard of care in Cameroon and Kenya. This protocol sets out in detail, the analysis and reporting procedures intended for the economic analyses to be undertaken alongside the INPUT trial.

2.2 Aim of the Trials

The trial aims to compare the cascade of care in two models for case detection and management of tuberculosis in children under the age of 5 years.

2.3 Objectives of the trials

The primary objective of this study is to assess the effect of integrating TB screening and diagnosis services in child health care services compared to standard of care in the second level hospitals (hubs) and their attached health centres (spokes), on the proportion of TB cases diagnosed among children <5 years old (the number of children who are clinically or bacteriologically diagnosed with TB over the total number of children attending the child healthcare services).

The secondary objectives of the trial are to;

- compare the outcomes of the intervention (integrating TB services intervention into child health care services) compared to standard of care in terms of the cascade of care measured by diagnosis of drug sensitive tuberculosis (DS-TB), treatment initiation and completion, overall and disaggregated by paediatric health services and level of care.
- determine the number of children needed to screen in order to diagnose one paediatric TB case through integration of TB services in various child health services.

2.4 Trial population

All children with presumptive TB who are eligible and whose parent/caregiver gives informed consent to participate until TB is excluded, enrolled in the prospective follow-up of the trial, will be included in the economic evaluation.

Enrolment criteria for the prospective follow-up will be:

- 1. Children < 5 years old.
- Presumptive pulmonary or extra-pulmonary TB case: symptoms or clinical signs suggestive of active TB disease. During the control phase, presumptive TB cases will be defined according to routine NTP protocols, whereas during the intervention phase a specific case detection tool will be used.
- 3. Other infectious diseases are not suspected or have already been ruled out.
- 4. Commitment to take treatment in the clinic of enrolment or another INPUT study site.
- 5. Parental/caregiver consent for the child to participate in the study.

Exclusion criteria will be:

- 1. Children too sick to participate in the study: in coma or with danger signs (drowsy, pulse rate more than 120 bpm, respiratory rate more than 32 cycles/per minutes), making it impossible or unethical to undergo consent process.
- 2. Children who are TB contacts but without symptoms or signs of active TB

2.5 Intervention and comparators

2.5.1 Integrated paediatric TB services – the intervention

The INPUT study will evaluate two major components of the CaP TB package;

- **Integration of TB screening** into all the child health care services with introduction of a specific case detection tool and updated presumptive TB register.
 - To improve symptom screening in the facilities, trained cough monitors will be placed in all the study sites. They will be lay health workers who screen patients in waiting rooms. They will physically accompany children with presumptive TB diagnosis to health care providers.
- Improvement of diagnosis capacities and their integration in all levels of care and all services:

- Introduction of a user-friendly diagnosis algorithm for the diagnosis of TB in children, especially at primary health care level, where capacities for biological diagnosis are often limited.
- Trainings for specimen collection, including gastric aspirates, induced sputum and lymph node aspiration, especially at district hospital level, with integration in the different paediatric entry points and in the inpatient ward for hospitalized children. All specimen will be tested with Xpert, on site or through referral of the sample to the Xpert site.
- Support for X-rays completion: use of transport vouchers for children to go to the referral site for x-ray if needed.

Children who are diagnosed with TB disease will be prescribed their treatment at the point of diagnosis. Drug dispensation, drug refill and follow-up will take place at the TB unit, in hub sites or as designed through routine system in the spokes site.

2.5.2 Paediatric TB services based on current routine approach (the national standard of care) – comparator

Although there are some differences in what constitute the standard of care, in both countries, TB care is currently delivered in a designated TB unit (or TB room/TB clinic/chest clinic). In most of the facilities, this is not a separated ward, just a specific room located in the facility (most of the time it is located within the HIV care unit in Kenya, whereas it stands alone but inside the facility premises in Cameroon). In Cameroon, low level of care sites do not currently include a TB clinic. While in Kenya screening is now recommended at every entry point; children and adults with presumptive diagnosis of TB all go to a TB unit for diagnostic work-up and treatment. In Cameroon, screening is not currently recommended nor done systematically at every entry point.

2.6 Trial design

The INPUT study is a multinational stepped wedge cluster-randomized intervention study designed to assess the impact of integrating TB services into child healthcare services on TB diagnosis capacities in children under 5 years of age in Cameroon and Kenya. These countries were purposively selected based on the TB burden, geographical location and representativeness of the epidemic in sub-Saharan Africa. Health centres were purposively selected based on their TB caseload and accessibility from the hub. Study sites were purposively selected in collaboration with the national TB program (NTPs) and ministry of health in Cameroon and Kenya which proposed a list of hospitals to undergo site assessment.

- The standard of care offers paediatric TB services based on current routine approach (national standard of care).
- The intervention will offer paediatric TB services integrated into key child healthcare services (maternal neonatal and child health (MNCH) services, under-5 clinic, paediatric outpatient services, nutrition services, paediatric antiretroviral therapy (ART) services and primary health care).

The planned total number of sites is 12 district (or sub-district) hospitals, 6 in each country with up to two purposively selected health centres (spokes) per district hospital (hub). A district or sub-district hospital (the hub) and one or two of its attached primary health care centres (spokes) that refer patients or samples to these facilities for TB diagnosis make up a cluster. Randomization will be stratified by country and done by a statistician based in the central research unit (CRU) who is blind to the clusters' characteristics other than the randomization variables. In each country, two sites will be allocated to cross into the intervention after four months under control phase, two after eight months under control phase.

2.7 Trial start and end dates

Recruitment for the trial started in May 2019 and is due to finish in October 2020. The follow-up period will run for 6-8 or 12-14 months depending on the nature of the TB disease and treatment response.

Section 3: Economic Approach

3.1 Aims of economic evaluations

The aim of the economic evaluation is to estimate the cost-effectiveness of integrating TB screening and diagnosis in children under 5 years of age into child healthcare services in comparison to the standard of care.

3.2 Objectives of economic evaluations

The primary objective is to estimate the long-term cost-effectiveness of the intervention in comparison to the standard of care for TB screening and diagnosis of child contacts over a lifetime horizon using economic modelling techniques. A secondary objective of the economic evaluation is to calculate the short-term cost-effectiveness of integrating TB screening and diagnosis in children under 5 years of age into child healthcare services in comparison to the standard of care over a 12-14-month maximum follow-up period in a within-trial economic evaluation.

3.3 Overview of economic analysis

The within-trial economic analysis will be performed using individual patient level data from the INPUT trial. The analytical approaches will take the form of cost-effectiveness, where, based on trial evidence, incremental cost-effectiveness (and cost-utility) ratios will be calculated by taking a ratio of the difference in the mean costs and mean effects (or utility measure).

3.4 Jurisdiction

The trial will be conducted in Cameroon and Kenya, mainly in public health facilities where health care services are primarily free of charge or highly subsidised at the point of use.

3.5 Perspectives

The primary economic analysis will be performed from the healthcare system's perspective (all direct medical and non-medical cost are included). We will also report data on the wealth quintiles of participants and their experience of coping with any costs associated with illness and care-seeking.

3.6 Time horizon

The primary economic analysis will compare the costs and health outcomes of each arm over a lifetime horizon using a mathematical model. A secondary analysis will compare the costs and outcomes over 12-14 months of follow-up (the maximum follow-up for the trial).

Section 4: Economic Data Collection and Management

4.1 Statistical software use for health economic analysis

The R language for statistical computing will be used for all data analyses.

4.2 Identification of resources

Pathway of care analysis through detailed review of the protocol, field visits and discussions with trial staff involved in the planning, implementation and coordination of the study was undertaken to identify all the individual components of TB diagnosis and treatment services involved in the two models of care. The following individual components were identified: days in hospital, facility (hospital or PHC) visits; sputum smear examinations; X-ray examinations; GeneXpert tests; overall supervision provided by EGPAF/CaP TB; drugs dispensed; visits to a TB focal person, training provided to healthcare workers, district, provincial and national programme management. In terms of the specific components of the intervention given in Section 2.5, the input of cough monitors is captured within facility visits and training, testing is captured within sputum examinations and GeneXpert tests and transport vouchers are within x-ray examinations. Subsequently all the activities and resources used in each component are identified. These include personnel, buildings, equipment, medications and consumables. All research related costs will be identified and excluded from the analysis. The amount of time and other resources utilized by parents /guardians will be incorporated into scenario analyses to provide a broader societal perspective of the resources associated with paediatric TB.

4.3 Measurement of resource use data

Primary data on the quantities of the individual components utilized in the pathway of care for each presumptive child TB case from the time of enrolment up to 12-14 months maximum follow-up will be collected prospectively using a case report form (CRF) designed for the trial and stored in an electronic database. These include the number of visits to healthcare facilities, number of sputum smears, number of X-rays, number of Xpert tests and type and quantity of drugs. The exact number and type of resources consumed in each individual component will be measured in physical units from expenditure records or through interviews with key facility personnel. Interviews will be performed with local EGPAF project staff to estimate staffing requirements for activities in the pathway of care. Data on the time spent by cough monitors and other staff in providing each service will be measured from the services directly using staff time sheets specifically designed for this study and supplemented with interviews with the relevant staff. For overall supervision, the number of people involved will be quantified and the proportion of their time spent on supervision identified. All equipment will be quantified and the proportion of time they are used for TB identified. For transport, the type of vehicles used, and the distances travelled per year, will be quantified. For facility visits, the type of staff working in the relevant departments will be quantified and the proportion of their time spent with TB patients quantified. Staff not involved in direct patient care, and the locations at which they work, will also be quantified. Non-personnel recurrent overhead expenditure will be quantified using expenditure records. Buildings will be quantified in terms of floor area. The amount of time and other resources spent by parents /guardians will be gathered retrospectively from a random sample of the study participants, via an interviewer administered questionnaire adapted from the WHO Global TB Programme's patient costs generic survey instrument[16].

4.4 Valuation of resource use data

All resource use will be valued in monetary terms using appropriate country specific unit costs. Unit costs for the different cost components e.g. health care facility visit, X-ray examination, sputum smear examination, Xpert test and medications will be based on quoted prices or on local financial data. Where these is not available, WHO-CHOICE and the wider literature will be used (with price level adjustment where necessary). When unavailable, a detailed ingredients-based costing exercise will be performed to derive them. Unit costs for other medicines, consumables and transportation costs will be obtained

from the study financial records. The total unit costs for each activity/visit will be the sum of the value of staff time, equipment, building space, transportation, consumables and overheads. The value of all direct services related to time will be estimated as the product of "hours of time" and "hourly wage". Information on staff salaries will be obtained from the study financial records or relevant MoH departments. Capital costs including building, equipment and vehicle costs will be calculated based on the current replacement costs and annualized at a discount rate of 3%. Both financial and economic costs will be captured, however only economic costs will be reported to capture the likely opportunity costs associated with the two models of care. All historical or retrospective costs will be adjusted for inflation using the relevant Consumer Price Indices. Unit prices will be gathered and reported in both the local currency and USD. Local currency costs will be converted to the USD currency using the relevant average exchange rates for reporting. Costs applied from other countries will be converted to their local equivalent using Power Parity indices.

4.5 Identification of outcomes

The health outcome measure will be the Disability-Adjusted Life Years (DALYs) quantified according to the WHO and Global Burden of Disease definition, as the sum of the years of life lost due to premature mortality in the population and the years lived with disability for people living with the health condition or its consequences.

4.6 Measurement of outcomes

Data on morbidity (active TB and sequelae) and the risk of mortality will be obtained from literature. Remaining life expectancy will be estimated using each country's age and sex-specific life table estimates.

4.7 Valuations of outcomes

The Global Burden of Disease (GBD) disability weights will applied to the patients' TB status to estimate the years lived with TB disease. Years of life lost will be estimated by summing the number of deaths at each age, multiplied by the number of years of life remaining. DALYs are obtained by summing these two metrics.

Section 5: Economic Data Analysis

5.1 Analysis population

The full analysis will include all child household contacts of TB index cases enrolled in the prospective follow-up of the trial.

5.2 Timing of analyses

The primary economic analysis will be performed when follow-up for all children is complete, maximum 12-14 months after enrolment, - the costs and health outcomes of each arm will be extrapolated beyond the trial over a lifetime horizon. A secondary analysis will be conducted as a with-in trial analysis at the end of the follow up period for the trial with no extrapolation.

5.3 Discount rates for costs and benefits

Costs and outcomes in the model extrapolation will be discounted at an annual rate of 3% as recommended by WHO-CHOICE[17] and the Gates/IDSi Reference Case for Economic Evaluation[18].

5.4 Cost-effectiveness threshold(s)

The primary economic analysis will use the published country-specific mid-point estimate of the opportunity-cost-based cost-effectiveness thresholds [19, 20]. The estimated mean DALYs and costs associated with each model of care will be combined with a feasible range of values for decision makers' willingness-to-pay (λ), to obtain the distribution of net benefits at different levels of λ .

5.5 Statistical decision rule(s)

The mean differences in costs, DALYs and net benefits between the treatment groups will be estimated with associated 95% uncertainty intervals.

5.6 Analysis of resource use

Differences in the use of resources/services between the two models of care will be described but not compared statistically.

5.7 Analysis of costs

The mean total costs, health care provider costs and patient costs, stratified by relevant patient characteristics (aged under 5 years, HIV/ART status, entry point) will be calculated using data for all children screened and cases found. A hierarchical generalised linear model (GLM) will be used for adjustment of baseline covariates and estimate the incremental cost of the intervention and 95% uncertainty interval, matching the analysis approach used for the main study outcomes.

5.8 Analysis of outcomes

Measures of intervention impact will be based on those reported by the trial where relevant. For cost outcomes, the statistical approach will follow those used for trial outcomes (ie mixed-effects modelling).

5.9 Data cleaning for analysis

Data cleaning will be undertaken using literate programming techniques and the reports made public.

5.10 Missing data

Missing economic data will be explored to determine the underlying prevalence, nature and patterns of "missingness", and if required the most appropriate imputation techniques will be used. For example, multiple imputation methods may be used if the data is missing at random (MAR). Results of any multiple imputation analyses will be compared to complete case analysis.

5.11 Analysis of cost-effectiveness

Cost and DALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the health care provider perspective.

We will separately report on wealth quintile of affected households, and the extent of dissaving as a result of disease and care-seeking.

Contingent on data availability, an extended cost-effectiveness analysis (ECEA) will be performed by incorporating risk protection benefits and providing a breakdown of costs, risk protection benefits and health benefits by wealth asset quintile.

5.12 Sampling uncertainty

The probabilistic sensitivity analysis will be used to determine the level of uncertainty surrounding the mean outcomes by generating at least 10,000 estimates of incremental costs and benefits, by applying the model to input parameters sampled from distributions describing their uncertainty.

5.13 Subgroup analyses/Analysis of heterogeneity

Additional analyses will be performed to investigate how cost and effect varies between different patient subgroups, namely: age (0-4 and 5-14); HIV status; socioeconomic status (DHS wealth quintile, contingent on data quality).

5.14 Sensitivity Analyses

Global sensitivity analysis will be used to compute sensitivity to parameters represented with distributions (either as partial rank correlation coefficients or approximate Sobol' indices). The impact of using different perspectives will be explored by performing a secondary analysis from a societal perspective i.e. including health sector and patient costs (direct costs and indirect costs will be collected). We will also explore the impact of using the per-capita Gross Domestic Product (GDP) for each country, which the World Health Organization (WHO CHOICE) suggests is a suitable willingness to pay threshold for determining whether an intervention is cost-effective[17]. The impact of no discounting or discounting using an annual discount rate that reflects the rate for government borrowings for costs and effects in each country will be explored in an additional analysis.

Section 6: Modelling and VOI Analyses

6.1 Extrapolation or Decision analytic modelling

Decision modelling will be used to evaluate the changes in costs and health on introducing the intervention. Modelling is necessary to extrapolate from trial outcomes on case-yield TB deaths averted and morbidity outcomes. Initial conceptual models will be iteratively refined in discussion with the trialists and the HEAP updated and published with the final detailed version before data becomes available.

6.2 Model type

The model will be a decision tree model representing the flow through from an index TB patient through to their outcomes. We will also develop statistical models to predict outcomes at each stage of care.

6.3 Model structure

The model will be broadly based on previously published simple models [21, 22]. The decision tree will be extended to include each of the relevant steps in the care cascade (facility visits, screening and diagnostics, treatment initiation, completion, etc) in order to calculate associated costs and model intervention effectiveness. Different types of facility (district hospital versus primary health care centre) will be explicitly modelled. The intervention will be represented as changes in the care cascade and

increases in the probability that children are screened and diagnosed with TB. The model will include child age, sex, and HIV/ART status, and model the natural history of progression to TB disease, TB treatment outcomes (as well as serious adverse events). Each country will be considered separately.

6.4 Treatment effect beyond the end of the trial

Treatment for active TB will not be assumed to affect long-term risks of developing TB.

6.5 Other key assumptions

The model will not be dynamic (i.e. accounting for indirect effects due to any reduction in TB transmission). We will assume that children under 5 are not infectious. We will use country-specific UN life-tables to estimate life-years lost. We will explore the potential impact of false-positives in scenario analysis compatible with outcomes and epidemiology.

6.6 Methods for identifying and estimating parameters

The majority of parameters will be characterised directly from trial or literature data. For example, parameters governing progression to disease and case-fatality will be as in previous models, i.e. based on literature reviews. We will systematically review the literature for data to support inclusion of TBM-related neurological sequelae. Parameters governing the effect of the trial in increasing linkage to care will be based on statistical models of the relevant step in the care cascade, based on trial data. Increase in case yield will be based on trial estimates, but we will incorporate evidence if differential effect by facility type in the analysis

6.7 Model uncertainty

All model parameters will be modelled as random variables to capture uncertainty. To quantify the impact of parameter uncertainty on model results, probabilistic sensitivity analysis will be conducted on all uncertain parameters by simultaneously sampling each parameter 10,000 times from their predefined probability distributions. The modelled incremental costs and health outcomes for each sampled parameter sets will be represented on a cost-effectiveness (CE) plane. These will also be used to construct a cost-effectiveness acceptability curve (CEAC) representing decision uncertainty surrounding cost-effectiveness. The CEAC will show the probability that each model of care is cost-effective at different threshold values a decision-maker is willing to pay for a specific health benefit (1 DALY averted).

6.8 Model validation

No specific validation procedure is anticipated.

6.9 Subgroup analyses/ Heterogeneity

The following sensitivity analyses are planned:

- If there is evidence to support an increased case-yield of TB beyond the target age-group through increased awareness, these benefits will included as a sensitivity analysis.
- Inclusion of benefits and costs relating to additional HIV diagnosis and ART, if there is evidence to support an effect.

Section 7: Reporting/Publishing

7.1 Reporting standards

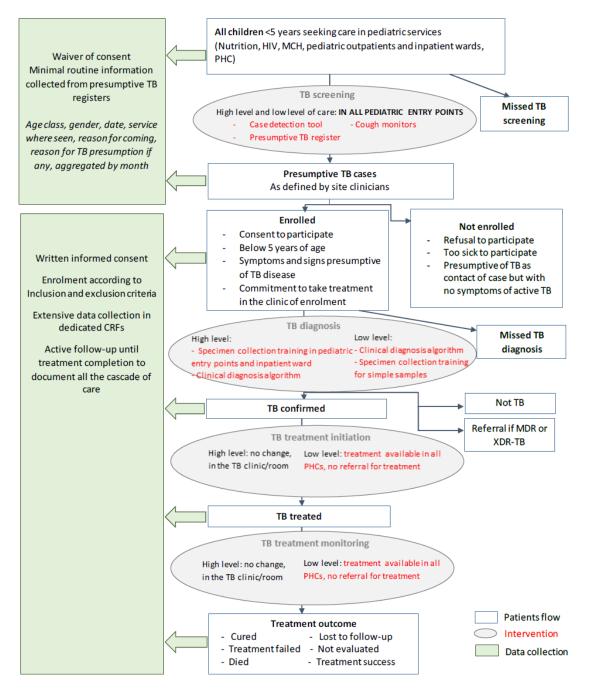
The CHEERS guidelines[23] will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers.

7.2 Reporting deviations from the HEAP

Any deviation from HEAP will be described and justified in the final published report and publicly posted with the HEAP on Zenodo.

Section 8: Appendices

8.1 Intervention flowchart



8.2 Health economic collection tools

8.2.1 Staff timesheets

8.2.1.1 Time sheet for capturing staff times at the facilities implementing Cap TB programme.

Date	Staff type (e.g. nurse, clinical	Please specify activity using attached	Start Time	Finish Time	CODES:
Dute	officer, medical doctor)	activity codes (i.e. 1-5)	Start Time	1 million 1 mile	TB Screening and diagnosis Activities
					The Servering and diagnosis Activities
20/04/19	Nurse	1	9.00	10.00	 Gastric aspiration Sputum induction
					3. Nasopharyngeal or laryngopharyngeal
					aspiration
					4. Fine needle aspirate
					5. Pleural aspirate
					_
					-
					-
					Netwo
					Notes:Record the time taken to obtain the sample
					including patient preparation, sample
					collection and any documentation that may be
					required.

Date	Staff type (e.g. CHV,	Please specify activity using attached activity	Start Time	Finish Time	CODES:
	nurse, CM)	codes (i.e. 1-8)			TB Contact Screening Activities
20/04/19	CHV	3	9.00	10.00	1. Communication with head of household
					2. Travel to/from household ^{\pm}
					3. Symptom-based contact screening*
					4. PT initiation*
					5. PT follow-up/drug refill*
					6. Other non-patient tasks – please specify
					(e.g administrative, research, training,
					meetings)
					_
					Non-Cap TB Specific Activities
					7. Other CaP TB-related activity – please
					specify
					8. Non-CaP TB-related activity
					-
					Notes:
					[¥] include any waiting times
CHV=com	munity health volunteer, Cl	M=cough monitor			

8.2.1.2 Time sheet for capturing staff times in the community-based TB contact tracing and management.

8.2.2 TB patient costs survey instrument

As a separate file, we include a patient cost survey instrument. The primary aim of this survey is to determine the proportion of households that resort to coping/dissaving as a result of TB illness and careseeking. This is a standalone piece of research that is outside the scope of this HEAP. However, data collected with this survey will be used to inform the societal perspective CEA and support a potential ECEA, hence inclusion of the instrument as a HEAP appendix. Tuberculosis patient cost surveys Version 1.0 August, 2018. (Adapted from WHO Generic survey instrument of December 21 2017).

Part I. Patient information to be obtained from INPUT database before the interview

Question	Answer categories (circle appropriate number or fill	Action for interviewer
	answer on the answer line)	The questions in part 1 are not part of the interview and should be pre- filled before the interview
1. Date of Interview	(Day/month/year)//	
2. Name of country		
3. Site ID		
4. Place of interview (facility name)		
<i>5.</i> Interviewer ID		
6. INPUT study ID Number		
<i>7.</i> Sex	1. Male 2. Female	
8. Age of participant:	2years	
9. Treatment registration group	Not MDR	If "Other", exclude from the study
	1. 1st line, new	
	2. 1st line, relapse	
	3. 1st line, re-treatment after loss to follow-up	
	4. 1st line, re-treatment after failure	
<i>10.</i> Start date of current TB treatment	(Day/month/year)//	
11. The patient is currently in intensive or	1. Intensive phase,days of phase completed	If patient has completed less than 14 days of the current treatment
continuation treatment phase?	2. Continuation phase,days of phase completed	phase, exclude, or postpone interview. Interview takes place after a minimum 14 days have been completed.
12. Currency used in interview:		report type of currency, e.g. USD

Tuberculosis patient cost surveys Version 1.0 August, 2018. (Adapted from WHO Generic survey instrument of December 21 2017).

Part II. Introduction to the participant

My name is ______ (name) and I work with Elizabeth Glaser Pediatric AIDS Foundation (EGPAF). EGPAF in collaboration with the MOH want to learn how much people spend before their children are diagnosed and when they treated for tuberculosis.

As we told you when you consented to take part in the INPUT study on PROVIDE DATE, we would like to ask you a few questions about the money you spend for the care of your child who has symptoms of tuberculosis. The interview will take around 45 minutes.

You may not answer these questions at any time, without telling us why you don't want to answer. Your answers will be kept confidential. I will ask you about your personal and your household's income. We will NOT share your answers with any tax or welfare authorities, even after the study has been completed.

The information that you give to us will be used for research only. It may also be shared with other researchers and writing papers, but all your personal information will first be deleted to keep your privacy and confidentiality. The information you give us will help us better understand how much it costs family to care for the sick child like the one in your situation.

Inclusion or exclusion								
Question	Answer categories (circle appropriate number or fill answer on the answer line)	Action for interviewer						
13. Decision about inclusion or exclusion	1. Included 2. Excluded	If included, skip to question 17						
14. If excluded, reason for exclusion	 No informed consent Treatment registration group is "other" (answer 6 in question 9) 	After completing this question, the survey is completed for this participant excluded from the survey.						
15. Interviewee identity	1. Parent 2. Guardian 3. Other (please specify)							

Out-of-pocket expenditure, reimbursements and time loss before and during TB diagnosis (before start of TB treatment)							
Question	Answer categories (check all that apply or fill answer on the answer line)	Instructions and actions for interviewer					
 16. Before your child(ren)'s TB treatment started at this facility, from which of the following types of facilities did you seek care or advice for symptoms of the current illness (including hospitalizations)? 17. How many weeks before starting TB treatment in the current facility did you visit each of these providers? 	1 st visit, provider type □ Weeks before treatment started: 2 nd visit, provider type □ Weeks before treatment started: 3 rd visit, provider type □ Weeks before treatment started: 4 th visit, provider type □ Weeks before treatment started: 5 th visit, provider type □ Weeks before treatment started: 6 th visit, provider type □ Weeks before treatment started: 7 th visit, provider type □ Weeks before treatment started: 8 th visit, provider type □ Weeks before treatment started: 9 th visit, provider type □ Weeks before treatment started: 9 th visit, provider type □ Weeks before treatment started:	 Enter in chronological order, using one of these provider categories for each visit, and entering how many weeks before TB treatment start each visit was. Remember to probe about informal care-seeking for example travelling to a grocery store to buy simple cough remedies or pain relief. Also report on table below. 1 Dispensary 2. Health Center 3. Sub county hospital 4. County hospital 5. National referral Hospital 6. Faith based hospital 7. Pharmacy / Drugstore 8. Herbalist / traditional healer 9. Private clinic 10. Private hospital 11. Community Health Worker 12. Spiritual healer 13. Other: 					
18. How much money and time did you spend for each of these visits before a TB diagnosis was given, including the visit when you actually received your diagnosis?	 See table below, and ask for each item Fill one line per visit For all that don't apply, mark/select NA Add more rows if more visits were made before starting cu Explanation of table headings: Visits: Includes outpatient visits as well as hospitalizations. Sho Type of provider: fill in provider type according to categories in Travel time: Hours spent to travel to and from facility Time spent for visit: Fill in hours for outpatient visits and hospi Day charge: Fees for hospital days. Only for hospitalizations, an fee, radiography etc.) Consultation fee: Other charges, not covered under day charge 	uld be filled in chronological order, 1st visit=visit 1. a question 19 where patient sought treatment or advice. talizations ad <u>only to be filled if not covered by the cost items below (consultation</u>					

Radiography and other imaging: out-of-pocket payments for imaging investigation (x-rays, CT-scan, ultrasound), TB-specific and other
Lab test fees: out-of-pocket payments for all tests, TB specific and others
Other procedures: out-of-pocket payments for biopsy, bronchial lavage etc. but not surgery unrelated to TB
Medicine fees: Any medicine (TB or other) prescribed before TB was diagnosed under NTP
Other, including nutritional supplements: any other treatments, such as nutritional supplements medically indicated
Travel: out-of-pocket payments for travel to the facility (does not include income loss), for both patient and any household member.
Food: out-of-pocket payments for additional food bought in relation to travelling the health care visit, and during visit or hospitalization,
for both patient and any household member
Accommodation: includes out-of-pocket payments related to renting a room/bed during health care visits, and any other non-medical
payments related to health care visit, for both patient and any household member
Out-of-pocket payments (gross): Direct payment made to health-care providers by individuals at the time of service use, i.e. excluding
prepayment for health services – for example in the form of taxes or specific insurance premiums or contributions. It is calculated as the
sum of direct medical (A) and direct non-medical (B) costs. If patient cannot remember the details of costs above, ask for the total out-
of-pocket payments of the visit, hospitalization.
Health insurance reimbursement: amount reimbursed to patient through medical insurance (private or social security) so far, does not
include expected future reimbursement
Out-of-pocket payment (net): medical and non-medical out-of-pocket payments minus reimbursements.

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				Medical out-of-pocket payments, (Total per visit) (A)							(Total per v (B)			Out-of- pocket payments (A+B) (Gross)		Out-of- pocket payments per stay (A+B-C) (Net)	
Visit	Type of	Travel	Time	Day charges (for	Consul-			Other pro- cedures	Medicines		Travel			Nutritional upplement		Total out- of-pocket	Health	
	provider (see list)	time (Hours):	spent for visit	hospitalizations only)	tation ree	graphy and other		cedures		payments, total		during health	dation B3	s		payments	reimburse	
		((Hours):	A1		imaging				to tai		care visit		B4	роскет	(ΣA1-7) +	ment	
					A2	A3	A4	A5	A6	ΣΑ1-7	B1	or hospital			payments (Total)	(ΣB1-3)		
												stay B2			ΣB1-3			
1 st																		
2 nd																		
3 rd																		
4 th																		
5 th																		
6 th																		
7 th																		
8 th																		
9 th																		
10 th																		

Part IV. Cost during current TB treatment (to be filled for all children on TB treatment) Unless specified, this section refers to the child's current treatment phase ONLY								
Question	Answer categories (check all that apply or fill answer on the answer line)	Instructions and actions for interviewer						
19. Is(are) your child(ren) currently hospitalized?	1. Yes 2. No	If yes, the cost data collected applies to the first row of the table question 16						
20. Have they been previously hospitalized <u>during their current</u> <u>TB treatment phase</u> and because of TB?	1. YesTimes 2. No	 Concerns only hospitalization during the current treatment phase: Does not include hospitalization before the current treatment started: For new cases, hospitalizations prior to TB treatment started should be filled in part III. If answer to both question 22 and 23 are "no", then skip to question 25. 						
21. About how much money and time did you spend for each of these hospitalizations?	 See table below, and ask for each item. Fill one line per hospitalization. Explanation of table headings: Type of hospital: fill in provider type according to categories in question 12 Number of days hospitalized: includes outpatient visits as well as hospitalizations. Should be filled in chronological order Day charges: total fees for hospital days for whole hospitalization in total. Only to be filled if not covered by the cost items below Consultation fee: other charges, not covered under day charge, including direct payment to health care staff Radiography and other imaging: any imaging investigation (x-rays, CT-scan, ultrasound), TB-specific and other Lab test fees: includes all tests, TB specific and others, including cost of transporting samples, if paid by patient Other procedures: includes biopsy, bronchial lavage, etc. but not surgery unrelated to TB Medicine to treat TB: fees for TB medicines only, bought inside or outside hospital Other medicines, including nutritional supplements: any other medicine, including nutritional supplements Travel: out-of-pocket payment for travel to the facility (does not include income loss), for both patient and any household member. Food: out-of-pocket payment for food bought in relation to travelling to and during the hospitalization, patient and household member. Other, including accommodation: payments related to renting a room/bed during health care visits and any other non-medical expenses for patient and household member. Out-of-pocket payments (gross): It is the sum of out-of-pocket medical and non-medical. If patient cannot remember the details of payments above, or has a hospital bill for all costs combined, ask for the total out-of-pocket payment for the hos							

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												(=)						
				Medical out-of-pocket payments,				N			ocket paym	ents,	Out-of-	(C)	Out-of-			
				(Total per visit)			(Total per visit)			pocket		pocket						
							(A)						(B)			payments		payments
																(A+B)		per stay
																(Gross)		(A+B-C)
																		(Net)
Visit	Type of	Travel	Time	Day charges (for	Consul-	Radio-	Lab tests	Other pro-	Medicines	Medical	Travel	Food	Accommo	Nutritional		Total out-	Health	
	provider	time	spent for	hospitalizations	tation fee	graphy and		cedures		payments,		during	dation	upplement	medical	of-pocket	insurance	
	(see list)	(Hours):	visit	only)		other				total		health	B3	S	out-of-	payments	reimburse	
	`,	. ,	(Hours):	A1		imaging						care visit		B4	pocket	(ΣA1-7) +	ment	
			(<i>)</i>		A2	A3	A4	A5	A6	ΣA1-7	B1	pr hospita			payments	(ΣB1-3)		
						1.0						stay			(Total)			
												B2			ΣB1-3			
1 st																		
2 nd																		
3 rd																		
4 th																		
5 th																		
6 th																		
7 th																		
8 th																		
9 th																		
10 th																		

Other costs during the current TB treatment (to be filled for all children)						
Costs fo	Costs for drug administration during TB treatment					
Question	Answer categories (check all that apply or fill answer on the answer line)	Action for interviewer				
22. On a daily basis, does the child currently take their TB medicines without supervision or support (self-administered) or does someone in your household supervise or support them?	 Self-administered Caregiver-supported administration 	 Who is responsible for supervision of daily intake of medicines, i.e, what is done every day. These questions are not referring to less frequent trips to pick up drugs (e.g., weekly), which are explored from question 31 onwards. 				
23. If supervised/supported, how many times a week?		The maximum will be 7 times a week				
24. If supervised/supported, who is providing supervision/support?	 Parent/guardian Health Care Worker Community health worker/ volunteer Family member/Relative/HH member/Friend 					
25. Was there a fee paid to the caregiver-supported administration?	1. Yes If yes, amount: 2. No					

Cost during outpatient visits for medical follow-up (see the doctor or nurse, have tests)					
Question	Answer categories (check all that apply or fill answer on the answer line)	Action for interviewer			
26. Do you or a household member accompany your child(ren)'s TB treatment medical follow-up visits?	1. Yes. 2. No	This should be filled if a household member accompany a child or children to TB PT follow-up visits when they see a clinician. If no, skip to question 39			
27. If yes, how often do you or a household member accompany your child(ren)'s TB treatment medical follow-up visits?	Every week Every 2 weeks Every month Other				

28. How many TB treatment medical follow-up visits has the child had so		This concerns clinical check-up, follow up, TPT medicines pick-
far <u>during this treatment (</u> to see the doctor or nurse, have follow- up tests, etc.)?		up and additional visits due to side effects or other TB related issues.
29. How long did the last follow-up medical outpatient visit take, including travel time and waiting time (total turnaround time)?	hours	
30. What was the cost of transport (return) at the last follow-up medical outpatient visit, including parking, in total for the child, you and/or any accompanying household member?		Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
31. What accommodation cost did you have for the last visit, in total, for the child, you and/or any accompanying household member?		Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
32. What fees did you pay during the last follow-up medical outpatient visit for <u>registration/consultation</u> ?	Registration/consultation fee	Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
33. What fees did you pay during the last follow-up medical outpatient visit for <u>radiography and other imaging</u> ?		See table above for explanations
34. What fees did you pay during the last follow-up medical outpatient visit for tests, TB tests and others?	Fees for tests	Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
35. What fees did you pay during the last follow-up medical outpatient visit for <u>other procedures</u> ?		Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
36. What fees did you pay at the last follow-up medical outpatient visit for non- <u>TB medicines</u> , including prescriptions for medicines bought outside the facility?	Drug fees	Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
37. What fees did you pay during the last follow-up medical outpatient visit for <u>other medicines</u> , including nutritional supplements?		Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit
38. What <u>other fees</u> not listed in the previous questions did you pay during the last follow-up medical outpatient visit?	Other fees	Cost related to the latest visit. If the interview takes place at the end of such a visit use the costs for the present visit and provide local examples

Costs for nutritional/food supplements					
39. Do you buy any nutritional supplements <u>outside of your regular diet</u> because of the TB illness, for example vitamins by health care staff?	1. Yes 2. No	If no, skip to question 55			
40. If yes, how much did you spend on these nutritional supplements in the past week approximately?					
41. Do you buy any additional food <u>outside of your regular diet</u> because of the TB illness, for example meat, energy drinks, or fruits as recommended by health care staff?	1. Yes 2. No	If no, skip to question 57			

42. If yes, how much did you spend on this additional food in the past	
week approximately?	

Health insurance scheme					
Question	Answer categories (check all that apply or fill answer on the answer line)	Action for interviewer			
43. Do you have any of the following health insurance types?	 National Health Insurance Fund (NHIF) Medical allowance Community based health insurance Private health insurance Other (specify) employment-based medical insurance None of the above 				

Social position					
Question	Answer categories (circle the most	Action for interviewer			
	appropriate or fill answer on the answer line)	These questions concern the guardian			
44. What is your education level?	 Not attended Nursery Primary school Post primary / vocational Secondary school College (middle level) University Other 	This question is for the guardian.			
45. What is your main occupation?	8. Other 1. Unemployed 2. Formal paid work 3. Informal paid work 4. Retired 5. Student	This question is for the guardian.			

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	6. Other (specify)	
46. What was your primary employment, or normal work, or normal other main activity before your child contracted TB?	 Unemployed Formal paid work Informal paid work Retired Student Other (specify) 	This question is for the guardian. This refers to the time before TB symptoms developed. Name all options first
47. What is your primary employment, or normal work, or normal other main activity now?	 Unemployed Formal paid work Informal paid work Retired Student Other (specify) 	This question is for the guardian.
	conomic status Index questions.	
48. What is the main source of drinking water for members of your household?	 piped into dwelling piped into yard/plot public tap/standpipe tube well or borehole protected well unprotected well protected spring unprotected spring rainwater tanker truck cart with small tank surface water (river/dam/lake/pond/steam/canal /irrigation channel) bottled water other 	
49. Do you do anything to the water to make it safer to drink?	 Yes No Don't know 	
50. Do you share a toilet facility with other households?	1. Yes 2. No	

51. Including your own household, how many households use this	No. households if less than 10	
facility?	10 or more	
	Don't know	
52. Is the cooking usually done in the house, in a separate building, or	1. In the house	
outdoors?	2. In a separate building	
	3. Outdoors	
53. Do you have a separate room that is used as a kitchen?	Yes	
	No	
54. How many rooms in the house are used for sleeping?		
55. How many of the following animals does this household own?	1. Cows/bulls	
	2. Other cattle	
	3. horses/donkeys/mules	
	4. goats	
	5. sheep	
	6. chickens/poultry	
56. How many people usually live in this household?		
50. How many people usually live in this household:		
57. How many children under 15 years of age usually live in this		
household?		
	Income (reported) before TB	
58. Are you the person mainly responsible for taking care of the child or	1. Yes 2. No	If No please skip to Question 75
children diagnosed with TB?		· · · · · · · · · · · · · · · · · · ·
59. Were you the person who earned the highest income in your	1. Yes 2. No	This question is for the guardian.
household before anyone in your household contracted TB?		
60. How many hours a week were you working before TB in your		This question is for the guardian.
household?	hours	This refers to the time before TB symptoms developed.
61. If you were in paid work, how much do you estimate your net income		This question is for the guardian.
from labour related activities, per month was <u>before TB in your</u>		For seasonal workers who experience fluctuating wages, try to
household?		ascertain an average monthly income for this question.
62. How much do you estimate the net income from labour related		Refers to all persons in the household.
activities of your household was per month, <u>before TB in your</u>		For seasonal workers who experience fluctuating wages, try to
household?		ascertain an average monthly income for this question.
(All family member's income must be counted)		

Income changes and social consequences					
Question	Answer categories (circle the most appropriate or fill answer on the answer line)	Action for interviewer These questions concern the guardian			
63. If you are in paid work, how much do you estimate net income from labour related activities, per month is now?		This question is for the guardian (ONLY ask if answer to question 71 is YES). In setting with an important informal sector you may not want to explicitly refer to taxes to make sure people are giving the right answer.			
64. How much do you estimate the net income from labour related activities of <u>your household</u> was per month, <u>at the time of a TB</u> <u>diagnosis?</u>		Refers to all persons in the household. For seasonal workers who experience fluctuating wages, try to ascertain an average monthly income for this question.			
65. How much do you estimate the net income from labour related activities of your household is per month <u>now</u> ?		Refers to all persons in the household For seasonal workers who experience fluctuating wages, try to ascertain an average monthly income for this question.			
66. How many hours per week are you working now?	hours	This question is for the guardian. (ONLY ask if answer to question 71 is YES).			
67. Approximately how many working days of income have you lost due to your TB illness overall?	days	(ONLY ask if answer to question 71 is YES).Working days of income: e.g., if a patient was not able to work for 5 half days and lost income for these, the number of days lost is 0.5*5=2.5. Report for total TB episode, incl. all days before and after job loss.			
68. Did you or your household receive any social welfare payment after you were diagnosed with TB? If yes, what type and amount during the last month?	0. No 1. Option 1per month 2. Option 2per month 3. Option 3per month 4. Option 4per month	 This question is for the guardian. Categories according to the following categories 1. Paid sick leave 2. Cash transfer for the vulnerable (specify, elderly, OVC, MDR, disability,) 3. Nutritional Support 4. Others (specify) In setting with an important informal sector you may not want to explicitly refer to taxes to make sure people are giving the right answer. 			

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	1. Yes	This question is for the guardian.
	a. Travel voucher:per month	More than one category allowed.
69. Do you currently receive vouchers or goods in kind to cope with TB	b. Food support:per month	
illness?	c. Other, enablers etcper	If no, skip to question 80
	month	
	2. No	
	1. Government	This question is for the guardian.
	2. NGO	
70. From whom do you receive the voucher/ goods	3. Employer	More than one answer allowed
	4. Private donation	
	5. Other	
71. How many adult and children regularly sleep in your house?		
(including patient, if variable, at time of diagnosis)		
72. How many rooms are there in the house excluding the bathroom?	#	
73. Has the TB illness affected your social or private life in any way?	1. No	More than one category allowed.
	2. Food insecurity	
	3. Divorce or Separated from	
	spouse/partner	
	4. Loss of Job	
	5. Interrupted schooling 6. Social exclusion	
	7. Other	

Coping				
Question	Answer categories (circle the most appropriate or fill answer on the answer line)	<i>Action for interviewer</i> <i>These questions are for the guardian.</i>		
74. How did you pay for any costs incurred since your child(ren) started TB treatment?	 Cash Community health insurance Given opportunity to pay later (credit) Waived/exempted Paid in kind NHIF Private insurance Don't know 	Multiple responses allowed.		

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75. If you paid by cash, where did you get the funds to pay for the services and how much was paid from each source [Record all that	1. Had own cash available -	Multiple responses allowed.
apply]	 Was given money by (friends, family members & relatives-No repayment was expected	
76. From whom did you borrow/receive?	 8. Don't Know (Enter 00) 1. Family 2. Neighbors/friends 3. Private bank 4. Cooperative 5. Employer 6. "Unofficial lender" (Black market) 7. Other 	Multiple responses allowed.
77. If you sold any assests, what did you sell?	 Land Livestock Transport/vehicle Household item Farm produce Gold/jewelry Other 	Multiple responses allowed. Circle all that are mentioned
78. How much money did you receive from the sale of all items of your property (in total)?		
79. The impact on your household financially since you experienced TB symptoms has been that your household became:	1 = Richer 2 = Unchanged 3 = Poorer 4 = Much poorer	

Thank you for your cooperation! Is there anything you would like to ask or say?

Comments by Interviewer:					
	[
Date (dd/mm/yyyy):	//	Signature interviewer:			

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