THE EAST AFRICA PUBLIC HEALTH LABORATORY NETWORKING (EAPHLN) PROJECT.

TITLE OF PROJECT:

EVALUATION OF THE IMPACT OF NEW TUBERCULOSIS DIAGNOSTICS ON PATIENT HEALTH OUTCOMES IN KENYA

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LIST OF ABBREVIATIONS

- **AFB**: Acid Fast Bacilli
- **CDR**: Case detection rate
- **DST**: Drug Susceptibility Testing
- **FM**: Fluorescent Microscopy
- **F/UP**: Follow up
- **HIV**: Human Immunodeficiency Virus
- **INH**: Isoniazid
- **KEMRI**: Kenya Medical Research Institute
- **LED**: Light Emitting Diode
- **LJ**: Lowenstein Jensen
- **MDR**: Multi-Drug Resistant
- **MGIT**: Mycobacterium Growth Indicator Tube
- **NTP**: National Tuberculosis program
- **OSSM**: Optimised smear microscopy
- **PTB**: Pulmonary Tuberculosis
- **RIF**: Rifampicin
- **Rx**: Treatment
- **STR**: Streptomycin
- **SLD**: Second line drugs
- **TB**: Tuberculosis
- **VCT**: Voluntary Counseling and Testing
- **XDR**: Extensively-Drug Resistant
- **ZN**: Ziehl Neelsen
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EAPHLN Project; TB Proposal – Kenya; Revised version 1.0 dated 19th July 2012.
SUMMARY

Tuberculosis (TB) is an important public health problem worldwide. The East African region bears the brunt of the TB burden. The countries in this region including, Kenya, Uganda, Tanzania, Rwanda and Burundi are among the 22 high TB burden countries with the incidence ranging between 157 and 353 per 100,000 population. The advent of HIV/AIDS has complicated the diagnosis and management of TB with associated emergence of MDR-TB and XDR-TB. In sub-Saharan Africa, TB diagnosis is made using Ziehl-Neelsen (ZN) microscopy. Due to its low sensitivity, ZN microscopy does not positively detect all TB cases among TB suspects thus increasing the number of false smear negative cases which subsequently leads to increased TB transmission. This study aims to evaluate the impact of new TB diagnostic tests on patient health outcomes in Kenya. This will be a quasi-experimental study involving rolling out of the new diagnostic tool combinations and observing increased case notification rates vs ZN, among other outcomes every subsequent year. The target population will be all pulmonary tuberculosis (PTB) suspects identified at satellite and non satellite sites in Kenya. Patients will be examined according to National TB Programme guidelines. A structured questionnaire will be administered to collect information about risk factors for development of TB. This will include: demographic data, contact with TB patient and previous history of TB disease among others. Each study site will enroll a study population in accordance to a study sampling strategy. Eligible participants will be requested to submit two sputum specimens. All specimens will be securely packed and transported to a study research laboratory in KEMRI by the fastest means available. Microscopy, culture and drug susceptibility testing will be done according to standard methods. Data will be entered into the computer using SPSS, version 11.5. Diagnostic test analysis, Odds ratios (OR) and their 95% confidence intervals (CI), will be estimated using binary logistic regression, with TB positivity as an outcome. Approvals will be sought from both SSC and ERC respectively. It is anticipated that findings from this study will help to detect more TB cases and hence contribute to a wider coverage of TB treatment and preventive services in Kenya. Accordingly, findings will contribute significantly to policy strategies on the management of TB cases.
1.0 INTRODUCTION AND BACKGROUND

The East African region bears the brunt of tuberculosis (TB) burden. The countries in this region namely Kenya, Uganda, Tanzania, Rwanda and Burundi are among the 22 high TB burden countries with the incidence ranging between 157 and 353 per 100,000 populations [WHO 2008]. Before the advent of HIV/AIDS, the incidence of TB was on the decline globally. Effective treatment is possible if TB infected persons are detected early and put on TB treatment immediately. However, the advent of HIV/AIDS has complicated the diagnosis and management of TB with associated emergence of MDR-TB and XDR-TB.

In sub-Saharan Africa sputum smear microscopy is the cornerstone for TB diagnosis especially at peripheral health services. This method is rapid and inexpensive and highly specific for *Mycobacterium tuberculosis* in high burden settings. However, the main limitation is its low and variable sensitivity, exacerbated in high HIV prevalence settings [Elliott AM, et al. 1993]. High TB-HIV co-infection rates and consequent low TB case detection rates impede disease control in many TB endemic settings, notably sub-Saharan Africa [WHO 2008]. In addition, sensitivity is largely determined by the duration of microscopic examination. Where workloads are high and the amount of time spent examining smears is low, sensitivity is correspondingly low [Cambanis A, et al. 2007].

A systematic review has shown that Fluorescent microscopy (FM) is on average 10% more sensitive than conventional light microscopy in detecting AFB in clinical specimens, has comparable specificity and takes significantly less time to read smears [Steingart K R, et al. et al. 2006] but requires technical experience.

Light emitting diodes (LEDs) for FM, commonly referred to as Optimized Sputum Smear Microscopy (OSSM) have been identified as an alternative to conventional FM for screening of *M. tuberculosis*[Anthony RM, et al. 2006, Marais BJ, et al. 2008]. LED lamps do not have the disadvantages the mercury vapor lamps have. Moreover, the life expectancy of LED lamps averages around 10-20 years of use and contrary to mercury vapor lamps, they do not explode after excessive usage [Anthony et al. 2006]. Since they require less power, they are also able to run on batteries [Van Deun A, et al. 2008, Affolabi D, et al. 2010, Anthony RM, et al. 2006]

TB culture method which is the gold standard takes long (4-8 weeks) before results are available and is not readily available in most settings. The most traditional approach in most countries, particularly in developing countries, is the use of the Löwenstein-Jensen (L-J) medium. The total turnaround time, including primary culture isolation followed by an indirect susceptibility test can be as long as 2 and even 3 months in many laboratories [Hart, CA. et al, 1996]. There is urgent need for laboratory infrastructure strengthening, development and evaluation of more sensitive and rapid TB diagnostics [Stop TB Partnership Retooling Task Force, 2008] to mitigate the spread of TB and especially MDR-TB.

Conventional methods such as the proportion method the absolute concentration method, and the resistance-ratio method [Canetti, 1969, Palomino, JC. 2008, 2010] are based on the measurement of growth on culture media containing antibiotics. But, the total turnaround time of an indirect susceptibility test on solid media can be reduced to 5-6 weeks, if primary culture isolation is carried out with the BACTEC system. If the BACTEC system is used for both isolation and subsequent indirect test with four first-line drugs, the time can be shortened to 3 weeks, on the average.

The BACTEC-960 (Becton-Dickinson Diagnostic Instrument System, Sparks, MD) was the first semi-automated system introduced for DST of *M. tuberculosis* in liquid medium. [Roberts G, et al, 1983, Siddiqui, et al, 1998, Benjamin W H, Jr et al, 1998]. The major advantage of this technique is that it is rapid, with the ability to detect growth and its inhibition earlier than by any other means.

New assays have been developed to detect resistance faster using genotype, rather than phenotype. The GenoType® MTBDRplus test is a deoxyribonucleic acid (DNA) strip assay polymerase chain reaction (PCR)-based and hybridization to detect mutations in the *inhA*, *katG*, and *rpoB* genes that confer INH and RIF resistance A recent meta-analysis found that the GenoType® MTBDRplus assay and one other similar commercial test have a pooled sensitivity of 98% for detecting RIF resistance and 89% for detecting INH resistance [Ling DI, et al, 2008]. Specificity averages 99% for RIF and INH [Ling DI, et al 2008]. Testing can be performed on isolates or AFB-positive sputum specimens and can return results in 8 hours, making this a promising tool to accelerate MDR-TB diagnosis and improve MDR-TB control. Although the GenoType® MTBDRplus assay has been studied in several laboratories, there is wide variation in circulating MTB strains across the globe and false negative results occur due to unique genetic mutations [Hillemann D, et al, 2005,. Evans J et al, 2009]. Validation in different settings is needed to ensure acceptable performance, particularly in Africa.
Impact of New Technologies

GeneXpert MTB/RIF, a fully automated molecular test for TB case detection and drug resistance testing was developed through collaboration in a public–private partnership. It is an automated molecular test for MTB detection and resistance to RIF identification, uses hemi-nested real-time PCR assay to amplify an MTB specific sequence of the *rpoB* gene, which is probed with molecular beacons for mutations within the rifampin-resistance determining region [Palomino JC, 2009; Urdea M, et al, 2006]. Testing is carried out on the GeneXpert MTB/RIF test platform, which integrates sample processing and PCR in a disposable plastic cartridge containing all reagents required for bacterial lysis, nucleic acid extraction, amplification, and amplicon detection [WHO/HTM/TB/2009.411]. The only manual step is the addition of a bactericidal buffer to sputum before transferring a defined volume to the cartridge. The GeneXpert MTB/RIF diagnostic test for MTB has recently been shown to have sensitivity and specificity comparable to culture in the diagnosis of pulmonary TB (92.2% and 99.2%, respectively) and MDR TB (99.1% and 100%, respectively) in a multi-country evaluation [WHO/HTM/TB/2009.411]. It is a closed-cartridge real-time PCR system which simultaneously identifies MTB and RIF resistance within 2 hours from a primary clinical specimen. The format of the test has several advantages over other commercial PCR-based diagnostics for TB. The closed cartridge format and minimal sample processing reduces the potential for contamination and allows the test to be performed by technicians not trained in molecular techniques, within a lab with basic infrastructure (such as a level II), while reducing time-to-result to 2 hours.

Considering the above description of all these new technologies, together with the recommendations from the WHO TB/HIV Working Group on Priority research questions for TB and TB/HIV in HIV-prevalent and resource-limited settings (WHO/HTM/TB/2010.8 and WHO/HTM/HIV/TB/2010.10), there is a need to conduct diagnostics evaluations that assess the impact of new diagnostics on patient important outcomes, including time to diagnosis, time to treatment, incremental value of new diagnostics, impact of new tests on clinician decision making, appropriateness of the treatment regimen offered on the basis of the diagnostic test result and impact of testing on treatment outcomes.

This proposal seeks to undertake a stepwise introduction of more sensitive and specific diagnostic methods that are rapid, accurate, accessible especially at peripheral health care facilities (satellite site) and with associated counseling of patients to enhance adherence and compliance to treatment (impact) for the laboratory network in Kenya and in the four countries supported by the World Bank for this project.

The impact evaluation approach is an assessment of how the intervention being evaluated affects outcomes, whether these effects are intended or unintended. In this study, it is used to determine efficacy and effectiveness of the introduction of the new diagnostics on the patient health outcomes. Therefore, impact in this study is defined as the “the attainment of development goals of the project, or rather the contributions to their attainment.” There is an important distinction...
between monitoring outcomes, which is a description of the factual (where you utilize the new diagnostics), compared with the counterfactual (where you do not utilize the new diagnostics) or attribute observed outcomes to the intervention. The proper analysis of impact requires a counterfactual of what those outcomes would have been in the absence of the intervention (World Bank, 2000).

Therefore, in this project, the impact of the new diagnostics on patient health outcomes will be measured by the attributes (unconfounded improvement in patient health outcomes due to the effect of intervention) attained not only by the introduction of the new diagnostic tools but also by improvement of both clinical and laboratory performance at the satellite sites. The problem of attribution is the problem of assigning observed changes in outputs and outcomes to the intervention. This is done by constructing a counterfactual. The counterfactual will be established by taking a comparison group (in this case a geographic area) which is identical to the intervention group (satellite), except that it is not subject to the intervention (non satellite).

1.1 STUDY JUSTIFICATION

In sub-Saharan Africa, TB diagnosis is made using Ziehl-Neelsen (ZN) microscopy. Due to its low sensitivity, ZN microscopy does not positively detect all TB cases among TB suspects thus increasing the number of false smear negative cases which subsequently leads to increased TB transmission. Therefore, there is a need to assess the impact of new diagnostics on patient health outcomes:

- Early and increased detection and proper management of TB patients
- time to diagnosis,
- time to treatment,
- incremental value of new diagnostics
- clinician decision making
- appropriateness of the treatment regimen offered on the basis of the diagnostic test result
- Waste of resources in empiric management of smear negative non TB
- Reduction in transmission, morbidity and mortality
  - impact of testing on transmission and treatment outcomes
- Data needed for policy change of TB diagnostics and surveillance.
- Improvement of satellite sites personnel performance.

1.2 BROAD RESEARCH QUESTION

What is the effectiveness and efficacy (impact) of introducing new TB diagnostics on patient health outcomes?

- Efficacy is the extent to which a specific intervention produces beneficial results under ideal condition (e.g., training of site personnel will result in improved patient health outcomes). Effectiveness is extent to which a specific intervention when deployed in the field in routine circumstances does what it is intended to do for a specific population (e.g.
introduction of new diagnostics will result in increased case detection.

1.2.1 SPECIFIC RESEARCH QUESTIONS

- What is the current status of TB testing in satellite and non satellite sites?
- What is the performance of different combinations of new TB diagnostic tests?
- Including (Gene Xpert, OSSM and Gene Xpert, OSSM, Gene Xpert and MGIT)
- What is the best fit algorithm for management of TB?

1.3 GENERAL OBJECTIVE

- To evaluate the impact of new TB diagnostic tests on patient health outcomes.

1.3.1 Specific objectives

1) To determine the diagnostic test values (sensitivity, specificity, positive and negative predictive test values) of new TB diagnostics (Gene Xpert; OSSM and Gene Xpert; OSSM, Gene Xpert and MGIT) vs ZN.
2) To determine the attributes (quality, cost effectiveness, user acceptability) associated with rolling-out new TB diagnostic combinations (using Step-wise approach).
3) To evaluate health care providers (clinical/laboratory) knowledge and practice before and after training.
4) To establish known factors such as socio-demographic, treatment seeking behavior, compliance to treatment associated with TB and MDR - TB detection.
5) To determine association between TB/MDR - TB case detection using different combination tests and exposure factors (e.g. HIV status)
6) To determine the evidence based best fit algorithm for management of TB.

1.4 STUDY VARIABLES/OUTCOMES

1. Primary outcome:(dependent variable)
   - Health outcome(diagnostic- case notification rates / cure rates),

2. Secondary outcomes (independent or predictor variables)
   - Time of onset of symptoms to treatment initiation
● Time from first presentation to the health facility to treatment initiation - logistics
● Determination of turn around time of laboratory results.
   ● time from first specimen submission to the health facility to laboratory results
   ● time from laboratory results to initiation of treatment by health care provider

3. Reasons for delay in patient presentation to health care facility, sputum specimen collection, laboratory results, laboratory results to health care provider (HCP) and HCP to treatment initiation.
4. MDR-TB diagnosis.
5. HIV positive/TB negative after study follow-up-integrate into HIV programme-
6. Deaths
7. Treatment success and failure rates
8. Quality-TB personnel performance
9. Cost effectiveness of the use of the new diagnostic tools due improvement
10. User acceptability of the new diagnostic capability especially for MDR -TB
2.0 METHODOLOGY

The study will involve Evaluation of the existing (ZN) and new diagnostics (GeneXpert, OSSM, MGIT) performance. The above objectives will be attained through the following activities:

1. **Objective 1**: validation of new TB diagnostics.
2. **Objective 2**: achievement of attributes associated with rolling out of new diagnostics will be obtained by conducting the following:
   a. To assess quality of laboratory results (use of internal and external IQC/EQA).
   b. Cost effectiveness sub-studies (offshoot proposals will be generated by personnel from satellite sites)
   c. Questionnaire-based studies for user acceptability assessment of new diagnostics by satellite sites (offshoot proposals from satellite sites)
   i. (b and c above are expected to be conducted using different protocols from this one during the period of this project. The proposals will be written by personnel from the satellite sites after being trained in research methodology and the number of proposals on respective topics will be captured using study M&E tool).
3. **Objective 3**: Train and assess change in health care personnel (clinical and laboratory) practices at satellite sites. This will be evaluated using a simple evaluation tool to be administered before and after training.
4. **Objectives 4**: Determine distribution of exposure factors in the study population.
5. **Objectives 5**: Link laboratory diagnostic results with patient exposure factors
6. **Objective 6**: Compare combinations of above objectives outcomes to select the best fit algorithm that provides optimum patient health outcomes i.e which diagnostic combination provides the most accurate and timely results, most cost effective and acceptable.

2.1 Study sites.

The satellite sites are health facilities which form a surveillance system which monitor cross border disease outbreak dynamics and they have been selected by countries based on EAPLN strategic considerations. The selection of non-satellite sites will be done by the individual countries based on these sites being non-adjacent to the satellite sites and separated by an administrative unit (i.e. district or county) to avoid contagion. *Contagion or contamination*: The comparison group is contaminated if it is subject to a similar intervention, either by spill-over effects from the intervention or another donor staring a similar project.
Figure 1: Example of sites selection from the four East African countries.

Source: Google map, 2012

TABLE 1: Showing selected satellite and non-satellite sites in Kenya

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<td>Narok</td>
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<td>Kitale</td>
<td>Nyahururu</td>
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<td>Busia</td>
<td>Kisii</td>
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<td>Malindi</td>
<td>Meru</td>
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2.2 Study population

All TB suspects identified during the study period will be recruited. These patients will be both new or retreatment cases attending the satellite and non-satellite sites with symptoms suggestive of TB (including cough of more or equal to 2 weeks) in accordance with the country NTP guidelines. Passive case detection rather than active case detection or contact tracing to specific high-risk groups, will be used to avoid any confounding or bias that could arise from such selection which is not currently routine. It is the ability to diagnose a case that is being investigated in this study.
2.2.1 Case definitions

The following definitions will be used to report individuals with TB:

- **TB case:** A tuberculosis (TB) case is the one who is positive on at least one of the following tests smear, GeneXpert and culture.

- **MDR TB:** A tuberculosis (TB) case with an *M. tuberculosis* complex isolate resistant to at least isoniazid and rifampicin.

- **XDR TB:** A tuberculosis (TB) case with an M. tuberculosis complex isolate resistant to at least isoniazid and rifampicin, as well as resistance to a second-line injectable drug (kanamycin, amikacin, or capreomycin) and a fluoroquinolone.

2.3 Study design:

Prospective quasi-experimental. The study will be done in two phases; namely

2.3.1 The validation phase

- This phase will only be done at baseline at year 1
- In this phase, samples with known ZN smear and GeneXpert results from Satellite sites and samples with known ZN smear results from non-Satellite sites will be analysed in the research lab using all the study new diagnostics
  - Samples from satellite sites will be used for specific diagnostic procedures as indicated in the study flow diagrams shown below in Figures 3, 4, and 5
  - Samples from non satellite sites will be used for QA/QC using ZN

- Three main reasons for validation are: i) to capture unique regional variations and ii) to have samples’ representative of country’s population iii) part of capacity building (training) for satellite sites staff

2.3.2 Quasi-experimental phase:

- The satellite sites will form the intervention arm (introduction of new diagnostic tools)
  - This will be done in a STEP-WISE process as indicated in Figure 1 below:
  - Other activities will include:
    - Training of TB personnel
    - Infrastructures and equipment installation
- The non-satellite site will continue with routine TB health care services with ZN diagnosis as indicated in Figure 2 below.

Monitoring and evaluation data will continuously be collected from both the satellite and non-Satellite sites using a standard M/E tool to be developed in collaboration with ECSA-HC.
**FIGURE 2: QUASI-EXPERIMENTAL DESIGN**

**Satellite site (Intervention arm)**

End of year 1 (Post-ZN+GeneXpert Intervention Evaluation /VALIDATION) → End year 2 (Post ZN+GeneXpert+OSSM intervention/Evaluation) → End year 3 (Post ZN+GenXpert+OSSM+MGIT Intervention/evaluation)

**Non satellite site (EQA)**

End of year 1 (Post-ZN intervention evaluation/VALIDATION) → End of year 2 (Post-ZN intervention evaluation) → End of year 3 (Post-ZN intervention evaluation)

Figure 2 indicates the process that will take place in both satellite sites (intervention site) and non satellite sites (no intervention site).

**EXPLANATION:**

- **Quasi-experimental design:** This is an evaluation design which address selection bias using statistical methods, rather than randomization. These methods model the selection process and so control for these variables in the analysis of outcomes.

- **Selection bias:** The beneficiaries of an intervention may be selected by some criteria (or select themselves) which is correlated with the observed outcome. Hence comparing outcomes of beneficiaries and non-beneficiaries can give misleading results. Where these criteria are not observed (i.e. there are no data on them), then there is a bias in the impact evaluation findings.

- **Quasi-experimental design description:**

  **Study type:** Step-Wise intervention  
  **Allocation:** Two arm selection with cluster sampling (sample for each site will be obtained from surrounding health centres-clusters-)
  **Endpoint classification:** Efficacy (diagnosis)/efficiency (TB personnel) study  
  **Intervention model:** Parallel assignment  
  **Masking:** Open label  
  **Primary purpose:** TB diagnosis
2.4 SAMPLE SIZE DETERMINATION

2.4.1 YEAR 1 (Bench-Mark stage: Initial ZN positivity)

The sample size for year 1 per site will be calculated according to the following formula:

\[ NC = \left( z_{1-\alpha/2} + z_{1-\beta} \right)^2 \times \sigma^2 \times (1+(c-1)\rho) \times \frac{DE}{\delta^2} \] {Formula No. 1}

Where:

- NC = sample size at year 1 per site.
- \( Z_{1-\alpha/2} = 1.96 \) for 5% significance and \( z_{1-\beta} = 1.28 \) for 80% power
- \( \sigma \) is the standard deviation of the case by TB suspects
- \( DE \) = design effect to adjust for intra-cluster correlation coefficient (\( \rho \)), which is normally estimated from previous studies.
- The TB suspect cases will be clustered into groups based on hospital records from the previous year depending on their health facility. This group of people is termed a cluster and the approach whereby sampling units are groups, and not individuals, is called clustered sampling. A design effect of 2 is used to inflate the sample size to cater for clustered sampling.
- \( c \) = the estimated number of clusters (surrounding health facilities) in the catchment area of the target site. The formula estimates the minimum sample size of the patients who will be visiting the facilities distributed across the \( c \) clusters.
- \( \delta \) = an error of margin. The relative precision is expressed as a percentage of the true prevalence itself in statistical terms the relative precision is translated into the required width of the 95% confidence interval around the TB PC/CNR.

2.4.2 Steps to sample size determination

An estimate of the Case Notification Rate (CNR) at study sites (Satellite and non satellite-

Data for TB suspects- from the previous year at the study sites and surrounding facilities will be obtained from respective laboratory records. These will be used to obtain the average proportion (PC) and standard deviation (SD) of TB suspects who are smear positive per site. This proportion is equivalent to CNR for that year and is calculated as follows:

(a) Number of persons who were TB suspects-N1.
(b) Number of people who were notifiable TB casesN2
PC=CNR=N2/N1.
TABLE 2a: Showing An Example Of Calculation of PC/CNR And SD from Data Obtained Directly From Satellite And Non-Satellite Sites In Kenya in 2010.

<table>
<thead>
<tr>
<th>SATELLITE SITES</th>
<th>NEW SUSPECTS</th>
<th>NO POSITIVE</th>
<th>% POSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUSIA DISTRICT</td>
<td>1919</td>
<td>217</td>
<td>11.31</td>
</tr>
<tr>
<td>MACHAKOS</td>
<td>2136</td>
<td>321</td>
<td>15.03</td>
</tr>
<tr>
<td>KITALE</td>
<td>2305</td>
<td>294</td>
<td>12.75</td>
</tr>
<tr>
<td>MALINDI</td>
<td>3129</td>
<td>237</td>
<td>7.57</td>
</tr>
<tr>
<td>WAJIR</td>
<td>1529</td>
<td>220</td>
<td>14.39</td>
</tr>
<tr>
<td>NON- SATELLITE SITES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERU</td>
<td>584</td>
<td>61</td>
<td>10.45</td>
</tr>
<tr>
<td>LAMU</td>
<td>88</td>
<td>10</td>
<td>11.36</td>
</tr>
<tr>
<td>NYAHURURU</td>
<td>554</td>
<td>72</td>
<td>13.0</td>
</tr>
<tr>
<td>NAROK SOUTH</td>
<td>841</td>
<td>126</td>
<td>14.98</td>
</tr>
<tr>
<td>KISII</td>
<td>2979</td>
<td>484</td>
<td>16.05</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRANDTOTAL</td>
<td>16064</td>
<td>2036</td>
<td>12.49</td>
</tr>
</tbody>
</table>

TABLE 2b: DESCRIPTIVE STATISTICS

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MINIMUM</th>
<th>MAXIMUM</th>
<th>PC%=MEAN</th>
<th>ΣSTD. DEVIATION</th>
<th>Σ²=VARIANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SATELLITE SITES</td>
<td>5</td>
<td>7.57</td>
<td>15.03</td>
<td>12.2100</td>
<td>2.97220</td>
<td>8.834</td>
</tr>
<tr>
<td>NON-SATELLITE SITES</td>
<td>5</td>
<td>10.45</td>
<td>16.05</td>
<td>13.1680</td>
<td>2.35976</td>
<td>5.568</td>
</tr>
</tbody>
</table>

NC=(Z_{1-\alpha/2} + Z_{\beta})^2 * \Sigma^2 * (1+(C-1)*P) * DE/ \Delta^2

NC1= SAMPLE SIZE FOR YEAR 1 FOR SATELLITE SITES
Σ²= VARIANCE OF SATELLITE SITES=8.8%
Z_{1-\alpha/2}=1.96
Z_{\beta}=1.28
C=NUMBER OF CLUSTERS =5
DE-DESIGN EFFECT =2
TABLE 2c: ANOVA

<table>
<thead>
<tr>
<th>Group</th>
<th>Sum of Squares</th>
<th>DF</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>2.294</td>
<td>1</td>
<td>2.294</td>
<td>.319</td>
<td>.588</td>
</tr>
<tr>
<td>Within Groups</td>
<td>57.610</td>
<td>8</td>
<td>7.201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59.904</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INTRA CLUSTER CORRELATION COEFFICIENT -

\[ p = \frac{\text{Variance between groups}}{\left(\frac{\text{Variance between groups (satellites and non satellites)}}{\text{+ Variance within groups)}}\right)} \]

\[ = \frac{2.29}{(2.29+7.2)} = 0.24 \]

NC1 = \((1.96+1.28)^2 \times 0.088 \times (1+(5-1) \times 0.24) \times 2 / (0.05)^2\)

\[ = 3.24 \times 3.24 \times 0.088 \times (1+0.96) / 0.0025 \]

\[ = 1435 \text{ participants for satellite site} \]

NC2 = \((1.96+1.28)^2 \times 0.056 \times (1+(5-1) \times 0.24) \times 2 / (0.05)^2\)

\[ = 3.24 \times 3.24 \times 0.056 \times (1+0.96) / 0.0025 \]

\[ = 913 \text{ participants per non-satellite site}. \]

NOTE: Suspect will be enrolled using systematic sampling for each year period (52 weeks): For instance:

- Enrollment for Satellite sites: NC1 will be \(1435/52\text{weeks} = 28\ \text{TB suspects per week per site.}\)
  - Sampling interval = \((\text{No of suspects per site per week} / 52\\text{(no. of weeks in a year)})/28\) for satellite sites

- Enrollment for non-Satellite sites: NC2 will be \(913/52\text{weeks} = 18\ \text{TB suspects per week per site.}\)
  - Sampling interval = \((\text{No of suspects per site per week} / 52\\text{(no. of weeks in a year)})/18\) for satellite sites
Sampling Interval Calculations per day

<table>
<thead>
<tr>
<th>Satellite</th>
<th>Suspects/site</th>
<th>Calculated interval</th>
<th>sampling</th>
<th>Sampling interval to be used per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUSIA DISTRICT</td>
<td>1919</td>
<td>1.317994505</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>MACHAKOS</td>
<td>2136</td>
<td>1.467032967</td>
<td></td>
<td>Every second suspect</td>
</tr>
<tr>
<td>KITALE</td>
<td>2305</td>
<td>1.583104396</td>
<td></td>
<td>Every second suspect</td>
</tr>
<tr>
<td>MALINDI</td>
<td>3129</td>
<td>2.149038462</td>
<td></td>
<td>Every second suspect</td>
</tr>
<tr>
<td>WAJIR</td>
<td>1529</td>
<td>1.050137363</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>NON- SATELLITE SITES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERU</td>
<td>584</td>
<td>0.623931624</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>LAMU</td>
<td>88</td>
<td>0.094017094</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>NYAHURURU</td>
<td>554</td>
<td>0.591880342</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>NAROK SOUTH</td>
<td>841</td>
<td>0.898504274</td>
<td></td>
<td>All suspects</td>
</tr>
<tr>
<td>KISII</td>
<td>2979</td>
<td>3.182692308</td>
<td></td>
<td>Every third suspect</td>
</tr>
</tbody>
</table>

For sampling intervals greater than one, the calculated figure should be rounded off to the nearest integer, but for sampling intervals less than one, every consecutive suspect patient should be recruited.

2.4.3 YEARS 2 AND YEAR 3

**TABLE 3:** shows sample size to be used in Years 2 and 3 in satellite and non-satellite sites based on year 1 sample size calculation.

<table>
<thead>
<tr>
<th>study year</th>
<th>sample size</th>
<th>sample size</th>
<th>Δ-delta</th>
<th>diagnostic tool at Satellite site</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satellite</td>
<td>Satellite</td>
<td>Non Satellite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year1</td>
<td>NC1 - Validation at Research lab</td>
<td>NC2 QA/QC</td>
<td></td>
<td>ZN – benchmark</td>
<td>pc-sensitivity of ZN</td>
</tr>
<tr>
<td>Year2</td>
<td>NC1</td>
<td>NC2</td>
<td>p1-pc</td>
<td>ZN +GeneXpert</td>
<td>p1</td>
</tr>
<tr>
<td>Year3</td>
<td>NC1</td>
<td>NC2</td>
<td>p2-pc</td>
<td>ZN +GeneXpert + OSSM</td>
<td>p2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p3-pc</td>
<td>ZN +GeneXpert + OSSM + MGIT</td>
<td>p3</td>
</tr>
<tr>
<td></td>
<td>NC1 =1435</td>
<td>NC2=913</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Δ-delta = expected improvement in the diagnostic sensitivity during roll out

PC values of subsequent years (year 3 and 4) will be calculated using ZN benchmark values of year two.
NOTE: Suspects will be enrolled using systematic sampling for each year period (52 weeks): For instance:

- Enrollment for Satellite sites; NC1 will be $1435/52$ weeks =$28$ TB suspects per week per site.
- Enrollment for non-Satellite sites; NC2 will be $913/52$ weeks =$18$ TB suspects per week per site.

2.4.4 Study activities
Validation study will use samples for year1 research labs-samples with known status from the field (satellite and non satellite labs) sample size based on the initial $\text{pc}\%$ values in year 1.
2.5 Patient Flow and follow-up

FIGURE 2: Summary of sample recruitment/processing and follow-up.

The above flow diagram illustrates the recruitment, HIV/TB testing and follow-up.

During follow-up both the current and subsequent test will be carried out to ensure no discrepancies arise from any differences.

Study flow diagrams for specific diagnostic procedure are shown below:

**GeneXpert alone vs ZN (FIGURE 3)**

All HIV positive PTB suspects will have their sputum samples tested for ZN microscopy and GeneXpert. GeneXpert positive and rifampicin sensitive patients will be treated with the first line regimen. Patients who will be GeneXpert positive but rifampicin resistant will be treated for MDR-TB and have a sample send for second line drug susceptibility testing at a laboratory with available facilities either within or outside the country. GeneXpert negative patients will be evaluated for other infections and followed up at 2, 4 and 6 months for TB.
FIGURE 3:

Note: Confirm all GeneXpert rifampicin resistant with conventional culture methods including LJ and or MGIT.
**OSSM and GeneXpert (FIGURE 4)**

Patients will be screened for symptoms of pulmonary TB, they will undergo HIV testing and ZN microscopy. If found smear positive they will be treated. However if they are smear negative and HIV positive they will have both OSSM and GeneXpert done on the first smear negative sample. Patients who then turn out to be both OSSM and GeneXpert negative will be investigated for other diseases through tests such as bacterial culture and others. These patients will be followed up at 2, 4 and 6 months to determine if they develop TB later.

**FIGURE 4 :**

**Note:** Confirm all GeneXpert rifampicin resistant with conventional culture methods including LJ and or MGIT.
OSSM + GeneXpert + MGIT (FIGURE 5)

All TB suspects will be tested for HIV, ZN and by LED microscopy. All smear positive patients will be treated for TB while smear negative HIV positive patients will have GeneXpert performed on their first sample. GeneXpert positive and rifampicin sensitive patients will be treated with the first line regimen. Patients who will be GeneXpert positive but rifampicin resistant will be treated for MDR-TB and have a sample sent for second line drug susceptibility testing. GeneXpert negative patients will have another sample sent for MGIT culture. MGIT MTB positive patients will be treated for TB while MGIT negative patients will be evaluated clinically and treated accordingly. Patients will be followed up at 2, 4 and 6 months to determine if they develop TB later.

FIGURE 5:
2.6 Inclusion, Exclusion Criteria and Data Collection

2.6.1 Inclusion criteria
- Patients aged 18 and above years, with suspected pulmonary TB, presenting to the study sites will be recruited into this study
- 6 month follow-up possible.
- Informed consent from relevant authorities and patients (annex 4)

2.6.2 Clinical procedures

The clinical team will be re-oriented on study procedures in the satellite sites.

2.6.2.1 General procedures:

At the patient registration center effort will be made to improve triage of patients to ensure that all eligible suspects are recruited. All systematic random/consecutive, eligible patients will be enrolled until the required sample size for each study site is reached.

2.6.2.2 Replacement of patients

Patients who qualify for enrollment in the study may be replaced at the same unit in the following circumstances:
- When they decline to consent to participate in the study
- When they fail to provide two sputum specimens within two consecutive days.

2.6.2.3 Patient registration

TB Coordinators or a study trained clinician (doctor, nurse, clinical officer) in the respective study site will be responsible for:-

(i) clinical diagnosis and selection of cases (clinical procedures will be the same as those used in the routine diagnosis of TB patients in each participating country).
(ii) filling of intake form (questionnaire) for each patient meeting the inclusion criteria and each patient enrolled shall be assigned a serial registration number with a prefix unique to the centre to permit identification at the diagnostic centre in case of a resistant strain or when additional information is required. Three forms will be filled for each patient.

a) a clinical form/questionnaire (annex 1)
   - This will include medical history and sociodemographic information, data on previous TB treatment of patients as well a physical examination for patients with unknown HIV status, a Provider Initiated Testing and
Counseling (PITC) will be carried out on informed consent and in accordance with country HIV/AIDS programme guidelines

- Three copies of the clinical form will be filled. One copy will be sent to the coordinating team, two copied should be kept at the diagnostic site, one at the OP and the other at the TB clinic if the patient becomes TB positive.

b) a sputum shipment form (annex 2)

- To be filled in duplicate at the laboratory/clinic from where the specimens/consignment will be sent: The form include the following information:
  - Facility patient code
  - Patient information (age, sex)
  - Date of collection of the sputum
  - Result of the smear examination
- One copy of the form will accompany the sputum specimens to the research lab and the second copy will be kept at the satellite/diagnostic center.

c) a laboratory result form (annex 3) –

- This form will be filled at the research lab and at the satellite lab whenever an intervention is made. A copy will be kept at the satellite/diagnostic center.

2.7 Clinic study registers:

A study register will be maintained by each clinic included in the study. The register will record all the patients enrolled in the study in a consecutive order. It will include patient code, name, age, sex, date of diagnosis, TB treatment initiation date, HIV test date and result, date of sputum sample, collection, and date samples were transported. This information will be collected from the TB laboratory register, TB register, and TB patient card. This register will be helpful to link the results obtained from the reference laboratory with individual patients, so that they can receive appropriate treatment. This register will not leave the health facility and will be the only link between the patient code and patients’ name.

2.7.1 Patient follow-up:

All TB patients will be followed up as per country program requirement. Smears will be done at month 2 and 5 as well as end of treatment to ascertain patient outcome. The study participants will be evaluated for outcomes such as failure, death, cure, default and treatment success.

HIV positive TB laboratory negative patients, , at any every stage of testing, will be followed up at 2, 4, and 6 months as indicated in Figure 3 and evaluated to determine their diagnosis.

The study group led by the Principal Investigator assisted by the OR Country Technical Working Group (OR_CTWG) will supervise the study in all participating sites to ensure that the laid down procedures are strictly followed.
Initial sputum smear microscopy at Satellite and Non Satellite Laboratories

Sputum samples from all suspects will initially be processed for smear microscopy at Satellite and Non Satellite Laboratories

- Taking into account distribution of satellite sites in each country, Samples may often need to be transported long distances to research laboratories. In this regard transport times for specimens must be kept to a maximum of five days, and ideally three or less days, to ensure valid culture examination.
- Any delay in processing samples requires samples to be kept at 4°C and processed within five days of specimen collection.
- A quality assurance system must be in place to ensure that all laboratories involved perform procedures proficiently, adequately and correctly.). Standardization of laboratory procedures (SOPs) is essential, particularly when more than one laboratory is involved.
- Training, re-training and monitoring of laboratory personnel during the study to ensure that staff follow procedures correctly and understand their role.

2.8 Laboratory Methods and Procedures

2.8.1 Sputum collection ZN microscopy, packaging and transportation

- Sputum specimens should be of adequate quantity (3–5 ml) and good quality. Clear instructions to participants on expectoration and good specimen production are critical. Ideally, people should be supervised to ensure the collection of a satisfactory specimen. Examination of induced sputum should not be used.
- Sputum specimen containers should be transparent, wide-mouthed, robust, leak-proof and screw capped and if possible sterile. Standard containers should used in all participating sites. They should preferably have a volume capacity of 50 ml and should allow both collection of the sputum sample in the field and decontamination and processing of the sample in the laboratory, thus decreasing the chances of culture contamination. The sputum container should be clearly labeled (the use of barcodes is encouraged) on the container – not on the lid – and packed correctly before transportation.
- Each sputum specimen will be examined for AFBs using ZN as soon as possible at the study site laboratory and results recorded in both laboratory register and study specimen shipment form before the samples are packed for shipment/transportation.

- The containers will be placed in a transport box and packed in material that will absorb any leakage. The sputum shipment forms will be sent with the specimen to the research laboratory.
2.8.2 Specimen handling

- The date and time of collection, laboratory reference number, facility patient code and A (spot) and B (overnight) (differentiating the two successive specimens from the same patient) would be written on the side of the container using a wax pen. The sputum samples will be stored in cool dark place. No decontaminant will be added. Where possible, the specimens would be kept refrigerated at 4°C before transportation to the research/reference laboratory. The containers will be placed in a transport box and packed in material that will absorb any leakage. The sputum shipment forms will be sent with the specimen to the reference laboratory.

- Standard operating procedure (SOP) will be followed for submission of sputum specimens by the satellite and non satellite sites to research/reference laboratory. The sputum shipment form will be completed for each patient and will be shipped along with the samples. A copy of the form will be kept at the study site. A log sheet with name and identification number for each specimen will be included with the shipped specimens.

2.8.3 Reception of sputum specimens at the TB laboratory

After registration of specimens in the laboratory, specimens should be visually inspected for leakage. If specimens are properly packed, leakage will stay inside the specimen bag and prevent contamination of other samples. If a specimen contaminates others, all affected specimens should be discarded to avoid cross-contamination and false-positive results. Specimens should only be removed from the specimen bags inside a biosafety cabinet (BSC).

- If a specimen has leaked but only within its own bag and enough sputum remains for processing, the outside of the container should be carefully disinfected using an appropriate disinfectant. The cap should be closed tightly and the tube must be clearly labelled again.

- If specimens have leaked and insufficient sputum remains for processing, the specimen container must remain unopened in its bag and be discarded directly into a biohazard waste bag for autoclaving or incineration. The field team should be notified in order to (i) take corrective action and prevent further leaks in the future, and (ii) collect replacement specimens from the same individual(s).

2.8.4 Training laboratory staff

All staff working with *M. TB* need to have adequate knowledge about high TB risk precautions. This is important to avoid the infection of laboratory workers.

- Furthermore, to ensure the reliability of results, it is also important that staff have enough background knowledge to understand each step in the SOPs.

- Staff knowledge and laboratory practices should be evaluated prior to and at the end of their training as well as monitoring of staff performance during the study
• This will include observation of practical procedures undertaken by each staff member and monitoring of the contamination rates of specimens processed by individual technicians.

• It cannot be assumed that experienced technicians will automatically have good laboratory techniques and have performed procedures according to the SOPs.

• All staff participating in the study will require some refresher training to ensure that all staff are following the same procedures. It is not advisable to introduce a technology that has not yet been implemented in routine practice immediately prior to the start of the study unless proper training is included, with adequate ongoing supervision, quality assurance (QA) and the ability to identify and resolve any problems encountered during implementation.

• Operational Research Technical Working Group will monitor the study site laboratories and ensure that study SOPs are being followed.

2.8.5 Laboratory supplies

• In the study, huge amounts of laboratory supplies are consumed per day due to the high number of specimens processed. Therefore, stock control of laboratory supplies needs to be well organized to ensure continuation of the work.

• A proper stock supply system needs to be put in place and one person should be responsible. A list needs to be prepared with the minimum amount of consumables to be in stock for a certain period.

• The amount of supplies needed depends on several factors including: (i) the expiry date; (ii) the availability in the country; (iii) the time between ordering and receiving consumables from abroad; and (iv) the availability of storage space including a cold room.

2.9 Mycobacteriology Laboratory Procedures:

The TB diagnostic procedures performed will depend on the diagnostic procedure being evaluated. There are three approaches being evaluated alongside the traditional ZN technique. These include:

i) GeneXpert alone
ii) Optimized smear Microscopy (OSSM) and GeneXpert
iii) OSSM + GeneXpert and MGIT

Specimens will be processed for smear microscopy, culture, identification, and drug susceptibility testing according to standard operating procedures.

2.9.1 ZN microscopy

At the satellite sites and Non Satellite sites as well as the research laboratory, each specimen will be tested by AFB sputum smear microscopy using ZN staining
2.9.2 Optimised Sputum Smear Microscopy (OSSM) LED microscopy
At the satellite site (intervention arm) as well as the research laboratory, each specimen will be tested by AFB sputum smear microscopy using LED microscopy.

2.9.3 Culture – MGIT and LJ
Sputum samples will be decontaminated and inoculated in MGIT tubes as well as two LJ slopes: one glycerol and one pyruvate Lowenstein Jensen (LJ) medium (pyruvate enhances growth of *M. bovis* and *M. africanum*) and incubated at 35-37°C up to 8 weeks. MGIT cultures will be incubated and read in a MGIT 960 machine while culture slants will be read for growth at 1, 2, 4, 6 and 8 weeks. Cultures negative at 8 weeks will be reported as negative.

2.9.4 Identification of M. tuberculosis –
All positive cultures (MGIT and LJ) will be confirmed for MTB complex by capilia test as per standard operating procedures.

2.9.5 GeneXpert
The first (spot) sample measuring at least 1 ml will be tested with GeneXpert following the standard operating procedures.

2.9.6 HIV testing:
Provider initiated testing and counseling (PITC) for HIV testing and counseling (HTC) is available at all health care facilities including out patient department and TB clinics. All TB suspects will be offered PITC as a part of TB/HIV collaborative activities. It is anticipated that TB registers will be modified to include HIV variable. This information will be collected and reported in accordance with specific country guidelines. Concerted efforts will be made to train TB staff at these sites on PITC as well as on integrated TB/HIV management.

2.9.7 Reporting of results and turn around time:
The microscopy, GeneXpert, culture, and drug DST results will be reported according to the national programme guidelines in addition to the standard Laboratory result form (annex 3). The date and time of dispatch of results from the laboratory will be recorded in the dispatch log to enable calculation of laboratory turn around time (TAT).

The attending/study clinician will receive results and ensure that patients receive appropriate treatment. The date and time of receipt of the results by clinician will be recorded in the clinical receipt log to enable calculation of the overall turn around time (TAT).

2.9.8 Archiving and storage of cultures
It is recommended to store aliquots of all sputum specimens as well as all confirmed isolates of *M.TB* isolated during the study in case additional or confirmatory testing is needed. A tracking system should maintained for all study specimens/isolates archived. The PI will be responsible of the archiving of all biological specimens and isolates.
2.9.9 Safety
Health education should be re-emphasized to all health care workers to minimize transmission within and without healthcare facilities.

- For all the laboratory work, a laboratory with appropriate, well-maintained biosafety facilities, and appropriately maintained and certified equipment (especially BSCS and centrifuges with safety buckets) must be in place before any work can start. Furthermore, all laboratory staff need access to appropriate personal protective equipment (PPE) including gloves (different sizes) and gowns.
- A safety manual needs to be in place describing all safety, emergency (such as how to handle spillage of live culture) and waste management regulations. This manual should be part of the learning materials during training. Sputum specimens are classified as biological materials, whereas live cultures are classified as infectious materials.
- Cultures of *M. TB* may only be handled in a class i or ii BSC within a certified containment facility with appropriate physical separation between functionally clean and dirty areas with proper airflow ventilation in place.
- All biological and infectious waste should be collected in biohazard labeled bags and burned, incinerated, or autoclaved.

Laboratory staff will be trained in the operation of the BSC and each BSC must be regularly maintained and certified annually to ensure proper performance.

2.9.10 Quality assurance
It is of great importance that a good internal quality control (IQC), and external quality assessment (EQA) system is in place. QC, and EQA help to measure human and/or assay error and allow assessment of whether clinical and laboratory results are trustworthy. This will be conducted using the following procedures:

**Examiner reliability:**

**Clinical:** Using quality assurance sampling for a total population of ten thousand TB suspects from the satellite sites with a minimum defective sample acceptable of 0 and a probability of defect accepted of 1% and an alpha of 5%, the sample size of repeatable samples is 262 for total patients for the satellite sites per year. This will give a sampling interval of approximately 50 patients for site per year. This translates to 1 randomly selected patient per site per week.

Matching will be done by the site clinical supervisor to ensure that every examiner is paired with another examiner so that the recommended number of matched results are obtained for each examiner. The results will be in custody of the site clinical supervisor and released quarterly to the study team. The number of which patient to be selected will be computer generated.

**Laboratory IQC and EQA on ZN smears and the new diagnostic tool(s):** At the end of every week, before dispatch of specimens collected during the week, the study laboratory site supervisor will blindly pick a random sample (using computer generated random numbers) of 50% positive ZN smears and 10% negatives ZN smears and they will be blindly read again by
the 1st reader to establish intra-reader reliability and 2nd reader to measure the inter-reader reliability. The laboratory supervisor to ensure the blindness of the reading will mask the identification of the slide (Gilpin C et al, 2007). The results will be in custody of the site laboratory supervisor and released quarterly to the study team. The same masked slides together with their corresponding specimens will securely packed and sent KEMRI, for EQA.

- EQA will be done during bench-mark stage and at every stage of intervention. Samples will be collected using a standard SOP from each participating site and sent to a designated KEMRI TB research laboratory for this activity.

2.9.11 Anticipated Study limitations

- At patient enrollment sites, there is limited experience in research skills. This is likely to affect accuracy and consistency in data collection. It is anticipated that training of personnel on operational research skills will minimize this short coming.

- Limited control of study site personnel by the study team may contribute to limited expected output. To overcome this aspect, attempts will be made to liaise with relevant authorities to minimize the study oriented staff turn over.

- Procurement of equipment as per study protocol may not be adhered to due to logistical issues. This may result in some variables not being measurable. For instance contamination of the study design by new tools being procured earlier or later than scheduled. The study team will make necessary adjustments during the data analysis stage controlling for any changes.

2.10 Data management and analysis

2.10.1. Data storage and archiving
All the paper based data will be indexed and filed in box files. The box files will stored in lockable cabinets for a period of up to five (5) years after completion of the study under the custody of the PI. The data will be shredded thereafter. For electronic records, password protected databases will be created and maintained throughout the study period with predetermined renewal period. Secondary data backup will be created weekly in compact disks (CDs) and external disks stored under lock and key by the PI.

2.10.2. Data Analysis
- Data entry will be done in MS Access and analysis using SPSS version 12. Descriptive statistics will be performed and data will be presented in tables, graphs and charts.
- Diagnostic test analysis will be done as illustrated in Figure 4
- Comparison of continuous variable will be done using student T-tests and ANOVA.
- Categorical variables will be compared using Chi-square tests.
Regression analysis will be carried out to determine factors predictive of CDR diagnostic performance in satellite and non-satellite arms and attribute improvement to introduction of new tools.

- Quality assurance during validation and roll-out of tools,
- Statistical analysis (diagnostic values of new tests with ZN as referent test).

**Outcome measures:**
- *Single difference:* the difference in the output or outcome either (1) before versus after the intervention, or (2) between project and comparison groups. Before versus after is not a good impact measure as it fails to control for other factors. The single difference project versus comparison groups fails to allow for differences between the two groups which may have existed prior to the intervention. The double difference takes care of these two problems. In the case where the determinants of participation are observed, then the bias can be removed using quasi-experimental methods.

<table>
<thead>
<tr>
<th>Combination of tests</th>
<th>ZN+ve</th>
<th>Combination of tests</th>
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</thead>
<tbody>
<tr>
<td>GeneXpert+ve OSSM+ve MGIT+ve</td>
<td>a-Sensitivity= a/(a+c) GeneXpert+ve OSSM+ve MGIT+ve</td>
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<tr>
<td>GeneXpert-ve OSSM-ve MGIT-ve</td>
<td>c-Predictive value= d/(d+c) GeneXpert-ve OSSM-ve MGIT-ve</td>
<td></td>
</tr>
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</table>

**2.11 Ethical considerations**

2.11.1. *Ethical approval:* Ethical approval will be obtained from KEMRI National Ethical Review Committee.

2.11.2. *Recruitment Plan:* Study Participants will sign Informed consent (annex 4) after an explanation of study procedures is done by a member of the study team. Requirement will be done after the informed consent has been sought.

2.11.3. *Confidentiality:* Participants should be assured that information that reveals the identity of any study participant shall not be released or published without consent.

2.11.4. *Potential Benefit:* The study will improve on the ability of the tests to detect TB and especially difficult to treat drug resistant TB early and might benefit you and the community with early treatment.
2.11.5. Anticipated Benefit: The long term benefit of the results from the study will provide information on the measures of efficacy and efficiency of the introduction of the new diagnostics.

2.11.6. Foreseeable Risk/ Harm and mitigation plan: There are no foreseeable risks or harm anticipated from participation in the study since the study is introducing improvement in the routine laboratory for TB diagnosis and no clinical new treatment procedures have been introduced.

2.11.7. Measures of Confidentiality of data: Strict confidentiality will be observed during the study and no information will be released or published without informed consent. The information will be known only to the study team member conducting the interview and to the medical personnel treating the patients. Protection of participant’s privacy will be done by the study team collecting minimal identification details from the participants solely for the purpose of matching laboratory results with clinical data. Serial participants’ identifier codes will be generated by the study team so that only the PI can perform the matching. The process will involve the use of pre-printed serial number stickers for each site to be placed on the clinical questionnaire, laboratory request forms and specimen containers specific for each participant.

2.11.8. Data ownership: The research is a property of KEMRI under the leadership of the Director, KEMRI.

2.11.9. Dissemination of study results: Findings from the study will be disseminated in peer-reviewed journals, scientific conferences and workshops.

2.11.10. Consent to publish: This will be obtained from the KEMRI Publication Committee prior to the release of any publication of study findings.
## 3.0 BUDGET

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<tr>
<th>ITEM</th>
<th>Activity</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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<td>Personnel</td>
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<td>3,350,000</td>
<td>3,750,000</td>
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<td></td>
<td>Study Team Members: 7 persons x Kshs. 6,000 per day x 10 days</td>
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<td>3,780,000</td>
<td>3,980,000</td>
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<td>Driver: 2 drivers x Kshs. 3,500 x 30 days</td>
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<td>7,340,000</td>
<td>8,020,000</td>
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<tr>
<td>Laboratory Expenses (reagents &amp; consumables)</td>
<td>ZN analysis (alone) 2,000 sample per year x Kshs. 1,750</td>
<td>3,500,000</td>
<td>3,500,000</td>
<td>3,500,000</td>
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<td></td>
<td>MIGIT (Zn, Gene-expert full test USD 40 per test) 15,600 samples x Kshs. 3,560</td>
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<td><strong>Sub-total 2</strong></td>
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<td>285,000</td>
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<td>Communication</td>
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<td>Sample transportation (kshs. 35,000 per week x 52 weeks)</td>
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<td>Maintenance</td>
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<td><strong>Sub-total (transport + maintenance)</strong></td>
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## 4.0 TIME FRAME

### Example Work plan: January 21012 to December 2015

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<td>Proposal development and project planning logistics</td>
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<td>• Main Research reference laboratory sites • Satellite sites • Non satellite sites</td>
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<td>• Main Research reference laboratory sites • Satellite sites • Non satellite sites</td>
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<td>5</td>
<td>• TRAINING of TB personnel from Satellite sites- on MGIT for patient recruitment and laboratory personnel. (before enrollment of patient). • ROLL OUT - MGIT • QUALITY ASSURANCE of ZN, Gene Xpert, OSSM and MGIT of site performance procedures with all specimens from satellite sites and non satellite sites. • QUALITY ASSURANCE of ZN of site performance procedures with all specimens from non satellite sites. • End year data analysis e.g. patient outcomes, • OR off shoot proposals from Satellite sites trainees • Final data analysis and report writing</td>
<td>• Main Research reference laboratory sites. • Satellite sites • Non satellite sites</td>
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5.0 ROLES OF INVESTIGATORS

Dr. Willie Githui: Principal Investigator, assumes overall direction and responsibility of all aspects of the study including proposal development, field and laboratory activities, safe custody of all study biological specimen / isolates, data as well as reports and manuscript preparation.

Dr. Thomas Ogaro: Co-investigator, responsible for field based activities including patient enrollment, sample collection and transportation, ensuring safety of field based data and participation in project reports and manuscript preparation.

Dr. Peter Wanzala: Co-investigator, responsible for the study design and sampling aspects, data management and reports and manuscript preparation.

Dr. Sabah Omar: Co-investigator, responsible for proposal development, reports and manuscript preparation.

Dr. Willy Sang: Co-investigator, responsible for proposal development, reports and manuscript preparation.

Dr. Michael Kiptoo: Co-investigator, responsible for training aspects, reports and manuscript preparation.

Mr. James Kariuki: Co-investigator, responsible for M&E tool development, reports and manuscript preparation.

Moses Mwangi: Co-investigator, responsible for M&E tool development implementation throughout the study period

Mr. Fred Orina: Co-investigator, responsible for Laboratory SOPs development, Laboratory based activities, reports, and manuscript preparation.

Ms. Kezia Evans: Co-investigator, responsible for laboratory activities, reports and manuscript preparation.

Mr. Peter Kinyanjui: Co-investigator, responsible for laboratory activities, reports and manuscript preparation.

Mr. Jeremiah Okari: Co-investigator, responsible for laboratory activities, reports and manuscript preparation.
6.0 REFERENCES


ANNEXURE

Annex 1: CLINICAL INFORMATION FORM

Country of origin……………………………
Name of Diagnostic site: ……………… Code………………

A: PATIENT IDENTIFICATION INFORMATION:

Name…………………………………………………………….
OP number……………CCC number ………………………………..
Patient unique No (Research team to generate)/Visit No. 0, 1, 2, 3, 4
Date Registered at OP (Day/Month/Yr) :……………………….

Sex: [M = male, F = female] :…………….
Age [In nearest whole years] :………………
Identification: Physical Address……………………………….
   Tel:…………………………………………..

TB Registration Number (if AFB Pos)………………….………..
Date Registered (Day/Month/Yr) :……………………………..

Relevant Country specific data: e.g country of origin, HIV Status, history of drug use etc [to be
deided on by country team]

B: MEDICAL HISTORY:

B1: Have you been treated for TB previously? [Y =yes, N = no] …………..
    If no, Go to B1.1, If yes, Go to B2.

B1.1 For how long have you been sick…?………………………………………..
B1.2 Did you seek treatment anywhere? Y/N………………………………………
B1.3 If Yes to above, where did you first seek treatment?…………………………………………………..
B1.4 Did you have these symptoms (Cough, night sweats, weight loss) prior to this episode?
    Y/N……………………
B1.5 Did you have Chest X-ray examinations prior to this episode?…………………
B1.6 Did you have sputum examinations prior to this episode?…………………
B1.7 Did you ever taken anti-tuberculosis drugs for more than one month?..
    B1.7.1 If yes, what was the name of the drug(s)?……………………………..
    B1.7.2 If they don’t know the name(s) {The clinician shows the TB card}………..
B1.8 Did you ever have injections for more than a month?…………………
B1.9 How long did you receive the injection (in months)?…………………

EAPHLN Project; TB Proposal – Kenya; Revised version 1.0 dated 19th July 2012.
B2: Information about previous TB treatment

B2.1 Where was the patient treated?……………………
B2.2 When was the patient treated?……………………
B2.3 How many times was the patient treated?………..
B2.4 Which drugs were used for treatment……………..
B2.5 Outcome of the last treatment according to the patient.

1. Cured: - :………
2. Treatment completed----------
3. Out of control (ooc/defaulter)-------
4. Failure ---------
5. unknown: ….……

C: MEDICAL RECORDS (If available)

C1 After extensive checking through the medical files and the other documents available in the health centre, have you discovered that the patient has been registered for tuberculosis treatment before?

Yes:…………. No:…………. No records:…………………..

If “Yes”, what was the outcome of the last course of chemotherapy?

1. Cured :……
2. Treatment completed : ………
3. Defaulted :……
4. Failed : ………
5. Transferred out : ………

C2. Is patient’s HIV status known?

Yes………………. No……………….

If Yes, Positive…………… Negative……………………

If No, test patient in accordance to standard guidelines

HIV test result: Positive: _________ Negative: _________

D: FINAL DECISION

D1: Patient has been previously been treated for TB for more than one month before
YES: ……… (answer to question B1 or B2)
NO: ……… (answer to question B1 and B2 and / or C was ‘no’)
Doubtful: …………

D2: If “Yes”, what was the outcome of previous treatment?

1. Cured / treatment completed : ………
2. Failed : ………
3. Defaulted : ………
4. Out of control(OOC)/defaulter not distinguishable: ………
5. Unknown : ………

E: DELAYS

According to programme guidelines and procedures for TB diagnosis

Indicate if there was delay in

E1: First presentation to health care facility more than 2 weeks from onset of symptoms
(YES) (NO)
If Yes (specify reason)…………………………………………………………

E2: Sputum specimen collection from 1st visit to facility to 1st sputum collection (same day)
(YES) (NO) (NB: Ask patient after receiving results)
If No (specify reason)…………………………………………………………

E3: Sputum collection to lab results (Same day as 2nd sputum collection) (YES) (NO)
(NB: Ask patient after receiving results)
If No (specify reason)…………………………………………………………

E4: Treatment initiation after results to HCP (If confirmed TB) (same day) (YES) (NO)
If No (specify reason)…………………………………………………………

Responsible Officer: ……………………………………………………………
Annex 2: Sputum Shipment Form

Country of origin: ........................................

Code of Diagnostic site: .............................................................

PATIENT IDENTIFICATION INFORMATION

Name of patient ............. Patient unique No........../Visit No. 0, 1, 2, 3, 4........

Laboratory Registration number............ TB Registration number (If AFB Pos)…..

Date registered: [Day/Mo/Yr] .........................

Sex:  Male: ............  Female: .......... 

Age [To nearest whole year]: ............

Date of sputum collection: A: (Spot).............  B: (Overnight) .............

Result of smear at study site: ..............................................................

B: SMEAR/GeneXpert

<table>
<thead>
<tr>
<th>SAMPLE Number</th>
<th>ZN</th>
<th>OSSM/LED</th>
<th>GeneXpertMTB/RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td>Time from sample reception to results (days)</td>
<td>Grade</td>
</tr>
<tr>
<td>Sample A</td>
<td>Positive</td>
<td>Positive</td>
<td>Detected</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Not Detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Invalid/Error</td>
</tr>
<tr>
<td>Sample B</td>
<td>Positive</td>
<td>Positive</td>
<td>Detected</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Not Detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Invalid/Error</td>
</tr>
</tbody>
</table>
Annex 3: Laboratory Results Form

Country Code: ………………..

Site Code: ………………. Patient unique No……./Visit No…….

A:  PATIENT

Patient Code …………………

HIV status: Positive (YES) …. (NO)…….

Date of specimen receipt at the research lab [Day/Mo/Yr] ………………………………..

B:  SMEAR/GeneXpert

Final ZN Smear results

Positive……………………. Negative……………………………..

Final LED Smear results

Positive……………………. Negative……………………………..

Final GENEXPERT results

MTB Positive (YES) (NO)RIF Positive (YES) (NO)

C: CULTURE

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>LJ</th>
<th>MGIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade Growth</td>
<td>Time from sample reception to results (days)</td>
</tr>
<tr>
<td>Sample A</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Contaminated</td>
<td>Contaminated</td>
</tr>
<tr>
<td>Sample B</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Contaminated</td>
<td>Contaminated</td>
</tr>
</tbody>
</table>
Final Culture results

LJ:
Positive………………. Negative……………….. Contaminated………………

MGIT:
Positive………………. Negative……………….. Contaminated………………

D: SPECIES IDENTIFICATION

Sample A:                      Sample B:

....... M. tuberculosis       ....... M. tuberculosis
....... M. bovis             ....... M. bovis
....... M. africanum         ....... M. africanum
....... Negative             ....... Negative
....... contaminated         ....... Contaminated
....... Other                ....... Other

E: DRUG SUSCEPTIBILITY TESTING (DST) TO FIRST LINE DRUGS

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>LJ</th>
<th>GeneXpert</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Results</td>
<td>INH</td>
</tr>
<tr>
<td>Sample</td>
<td>Sensitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contaminated</td>
<td></td>
</tr>
<tr>
<td>Time from specimen to results (hours)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Final DST results

Susceptible to:  

…… Isoniazid  
…… Rifampicin  
…… Ethambutol  
…… Streptomycin  

Resistant to:  

…… Isoniazid  
…… Rifampicin  
…… Ethambutol  
…… Streptomycin

Date of recording: [Day/Mo/Yr]:……………………..

Responsible Officer: ………………………………………………….
Annex 4: AN INFORMED CONSENT DOCUMENT

Study number: SSC No. 2281

Title of the research study:

EVALUATION OF IMPACT OF NEW TUBERCULOSIS DIAGNOSTICS ON PATIENT HEALTH OUTCOMES IN KENYA

Principal Investigator:
Dr. Willie Githui

Co- Investigators:
1. Dr. Thomas Ogaro
2. Dr. Peter Wanzala
3. Dr. Sabah Omar
4. Dr. Willy Sang
5. Dr. Michael Kiptoo
6. Mr. James Kariuki
7. Mr. Moses Mwangi
8. Mr. Fred Orina
9. Ms. Kezia Evans
10. Mr. Peter Kinyanjui
11. Mr. Jeremiah Okari

Collaborating Institutions:
1. Centre for Respiratory Diseases Research – CRDR
2. Division of TB, Leprosy & Lung Disease – DTLD
3. Centre for Public Health Research – CPHR
4. Centre for Geographic Medicine & Research, Coast – CGMRC Kilifi
5. Centre for Microbiology Research – CMR
6. Institute OF Tropical Medicine and Infectious Diseases - ITROMID
7. TB Central Reference Laboratory

Collaborators
1. Project Coordinating Unit (PCU), EAPHLN Project, Ministry of Public Health and Sanitation and Ministry of Medical Services
2. District Medical Officers of Health and Medical Superintendents of Busia, Kitale, Machakos, Malindi, Wajir, Narok, Nyahururu, Lamu, Meru and Kisii district hospitals
3. Heads of laboratory services in Busia, Kitale, Machakos, Malindi, Wajir, Narok,
Nyahururu, Lamu, Meru and Kisii district hospitals

**Study location:**

<table>
<thead>
<tr>
<th>SATELLITE SITES</th>
<th>PROPOSED NON SATELLITE SITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wajir</td>
<td>Lamu</td>
</tr>
<tr>
<td>2. Machakos</td>
<td>Narok South</td>
</tr>
<tr>
<td>3. Kitale</td>
<td>Nyahururu</td>
</tr>
<tr>
<td>4. Busia</td>
<td>Kisii</td>
</tr>
<tr>
<td>5. Malindi</td>
<td>Meru</td>
</tr>
</tbody>
</table>

**Purpose of the research:**

The purpose of the study is to determine if the introduction of new TB diagnostics at satellite sites will result in better TB patient health outcomes.

**Description of the Research:**

The study has enrolled you to investigate your coughing condition and will help us to know the best choice of confirm your disease.

**Procedures**

You have been identified as potential participant of this study. You will be asked questions for a duration of about 15 minutes to help in making the correct diagnosis. Information about you may also be obtained from your medical records. You may choose not to answer any question or withdraw at any time. If you choose to participate, you will also be requested to provide two sputum samples for laboratory examination. The first one you will provide immediately and the second one on the following morning. The study will also require you to undertake a HIV test as part of the investigations for proper management. About 1 milliliter of blood will be drawn from a finger prick. There will be a possibility of bruising during pricking at the site where blood is drawn but this will not be harmful. You will also be entitled to receive the study results. If follow-up is necessary from the results of the tests you will be requested for permission to be followed-up for up to a period of six months with a two months interval. Sputum samples will be
collected at each visit during the follow-up period. If diagnosed with TB you will be provided with the necessary full treatment for the required period. The study samples will be archived for future studies with your permission.

**Potential Harm, Injuries, Discomforts or Inconvenience, Risks:**

No harm or risk is anticipated from your participation in the study since the study is introducing improvement in the routine laboratory for TB diagnosis and no clinical new treatment procedures have been introduced.

**Potential Benefits:**

The study will improve on the ability of the tests to detect TB and especially difficult to treat drug resistant TB early and might benefit you and the community with early treatment.

**Anticipated Benefits:**

The long term benefit of the results from the study will provide information on the measures of efficacy and efficiency of the introduction of the new diagnostics.

**Alternative Procedures or Treatments:**

The study will not change the National TB testing algorithm but it is designed to strengthen the National TB programme with better diagnostics for TB

**Confidentiality**

Strict confidentiality will be observed during the study and no information will be released or published without informed consent. The information will be known only to the study team member conducting the interview and to the medical personnel treating you. You may contact the ethical review committee of KEMRI for any information of concern to you.

**Cost/payment**

After enrolment in the study, you will not be charged for clinic visits or treatment. You will not be paid for participation in the study.
Participation:
Your participation will be voluntary to assist in suspected TB disease diagnosis to enable early treatment. If you are found to have TB you will be managed appropriately until you are cured.

Withdrawal
Should you or your study doctors decide to withdraw your from the study; your will still be eligible for care according to the standard TB treatment procedures.

Use of the results
The findings from this study may be published in a medical journal. The study participants will not be identified by name. After the study is completed, you may request an explanation of the study results.

Treatment and compensation for injury
If you are injured or you have questions about injuries as a result your being in the study, please contact the doctors in the study clinic. The services at the public health facility will be open to you in case of any such injury. However, neither the principal investigator nor World Bank the sponsors of this study have a program to cover your costs if you are hurt or has other bad results.

Questions
This study has been explained to you and your questions were answered. If you have any other questions about your rights, FOR INFORMATION OR ANSWERS TO QUESTIONS CONCERNING YOUR RIGHTS AS A RESEARCH SUBJECT YOU MAY CONTACT: PRINCIPAL INVESTIGATORS: Dr. Willie Githui of KEMRI, Centre for Respiratory Diseases Research, P. O . Box 47855 00100- Nairobi, Tel No: +254 710 492533, E-mail:wgithui@yahoo.com or co – investigator, Dr. Thomas Ogaro, Tel No. +254 722 77 00 90, E-mail address: thomasogaro@yahoo.com

Official contact details for questions about: matters on rights i) to a participants’ participation ii) a research-related injury; and iii) the research study itself contact Secretary, KEMRI/National Ethics Review Committee, P. O. Box 54840 00200, Nairobi. Telephone 020 272 2541; 0722 205901; 0733 400003


Joining of your own free will

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to refuse to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are entitled.

What your signature or thumbprint means

Your signature or thumbprint below means that you understand the information given to you about your participation in the study and in this consent form. If you wish to participate in this study, you should sign or place your thumbprint below.
SAMPLE CONSENT FORM

The study you are about to participate in is to assist us in determining the best choice of TB diagnostic tests that will enable us to detect it early and make correct decisions about treatment. Should you agree to participate in the study, you will be asked to assist us fill in a questionnaire, collect sputum and have a HIV test done.

All data collected from you will be coded in order to protect your identity, if applicable. Only the research study staff will have access to the information. At the end of the study, there will be no way to link your name with your data. Any additional information about the study will be provided to you including the final study results.

You are free to withdraw or refuse to answer any question at any time without any consequences. Should you agree to participate in the study, please sign your name below, indicating that you have read and understood the nature of the study, your responsibilities as a study participant, the inconvenience associated with voluntary participation in the study and that all your questions and concerns concerning the study have been answered satisfactorily.

You will receive a copy of this signed consent form to take away with you.

__________________________________________  ______________________________________
Signature of the Study Participant and Date     Thumbprint of the study Participants and Date

__________________________________________
Signature of person Obtaining Consent and Date

__________________________________________
Signature of witness and Date
Kiambatanisho 5: HATI YA KUOMBA IDHINI

Kichwa Cha Utafiti:

TATHMINI YA ATHARI ZA VIFAA VIPYA VYA UCHUNGUZI WA KIFUA KIKUU KATIKA MATOKEO YA KIAFYA YA WAGONJWA NCHINI KENYA

Mchunguzi Mkuu
Daktari Willie Githui 1

Wachunguzi Washirika
1. Daktari Thomas Ogaro 2
2. Daktari Peter Wanzala 3
3. Daktari Sabah Omar 4
4. Daktari Willy Sang 5
5. Daktari Michael Kiptoo 6
6. Bwana James Kariuki 3
7. Bwana Moses Mwangi 3
8. Bwana Fred Orina 1
9. Bi. Kezia Evans 1
10. Bwana Peter Kinyanjui 1
11. Bwana Jeremiah Okari 7

Taasisi Zinazoshiriki
1. Kituo cha Utafiti wa Magonjwa ya Kupumua - CRDR
2. Idara ya Ukoma, Kifua Kikuu & Magonjwa ya Mapafu - DLTLD
3. Kituo cha Utafiti wa Afya ya Uma - CPHR
4. Kituo cha Tiba ya Kijiografia & Utafiti, Pwani – CGMRC
5. Kituo cha Utafiti wa Microbiolojia - CMR
6. Taasisi ya Tiba ya Kitropiki na Magonjwa ya Kuambukiza - ITROMID

Washirika

1. Kitengo cha kuratibu mradi (PCU), mradi wa EAPHLN, wizara ya afya ya uma na usafi wa mazingira.
2. Maafisa wa matibabu ya afya wa wilaya (Busia, Kitale, Machakos, Malindi, Wajir, Narok, Baringo, Lamu, Meru, na Kisii).
3. Wakuu wa huduma za maabara (Busia, Kitale, Machakos, Malindi, Wajir, Narok, Baringo, Lamu, Meru na Kisii).
**Maeneo ya Utafiti:**

<table>
<thead>
<tr>
<th>MAENEO YA SATELLITE</th>
<th>PENDKEZO LA MAENEO YASIYO YA SATELLITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. WAJIR</td>
<td>LAMU</td>
</tr>
<tr>
<td>2. MACHAKOS</td>
<td>NAROK</td>
</tr>
<tr>
<td>3. KITALE</td>
<td>KISII</td>
</tr>
<tr>
<td>4. BUSIA</td>
<td>SOUTH NYANZA</td>
</tr>
<tr>
<td>5. MALINDI</td>
<td>MERU</td>
</tr>
</tbody>
</table>

**Lengo la utafiti:**
Lengo la utafiti huu ni kuamua kama kuanzishwa kwa vifaa vipya vya uchunguzi wa kifua kikuu katika maeneo ya satellite italeta matokeo bora ya kiafya kwa wagonjwa wanaogua kifua kikuu

**Maelezo ya utafiti:**
Utafiti huu umekusajili wewe ili kuchunguza hali yako ya kukohoa na utatusaidia kujua chaguo bora kuthibitisha ugonjwa wako.

**Taratibu:**


**Uwezekano wa kutokea madhara, kuumia usumbufu au athari zozote:**
Hakutakuwa na madhara au hatari ambayo inaweza kutokea kwa kushiriki kwako katika huu utafiti kwa sababu huu mradi unalenga kuanzishwa kuboresha hali ya kugundua kifua kikuu kwenye mahabarana, hakuna taratibu mpya za matibabu zilizo
anzishwa.

Faida zinazoweza kutarajiwa:
Huu utafiti utaboresha uwezo wa vipimo kugundua kifua kikuu na haswa kutibu kifua kikuu sugu mapema na waweza kukufaidi wewe na jamii kwa matibabu ya mapema.

Faida zinazotarajiwa:
Faida za muda mrefu za matokeo ya utafiti zitataarifu juu ya hatua za ufanisi na ufanisi wa kuanzishwa kwa uchunguzi mpya.

Utaratibu ama matibabu mbadala
Utafiti huu hautapeana matibabu yasiyo ya kawaida lakini utasaidia kufanya uchunguzi wa mapema wa kugundua kifua kikuu

Usiri:
Usiri mkali utazingatiwa muda wote wa utafiti huu na hakuna habari itakayo tolewa au kuchapishwa una kifua kikuu utapata matibabu kikamifu mpaka upone.

Gharama/Malipo:
Baada ya kujianzishwa utafiti, hautalipishwa kuhudhuria Kliniki au kupata matibabu. Hautalipwa kwa ajili ya kuchunguza kifua kikuu kinachoshukiwa kwa mapema. Ukipatikana una kifua kikuu utapata matibabu kikamifu mpaka upone.

Kushiriki:
Kushiriki kwako ni kwa hiyari yako ili usaidie kuchunguza kifua kikuu kinachoshukiwa kwa mapema. Ukifanya una kifua kikuu utapata matibabu kikamifu mpaka upone.

Kujitoa
Ikibidi wewe au madaktari wako wa utafiti kuchunguza kutoka kwa utafiti; bado utastahili kufanya hawatatambuliwa kwa utafiti.

Matumizi ya matokeo
Matokeo ya utafiti huu yanaweza kuamua katika jarida la matibabu. Washiriki kweno wa utafiti hawataamuliwa kwa majina. Baada ya utafiti kukamilika, unaweza kuomba kuelezewa matokeo ya utafiti.

Tiba na fidia kwa majeraha
Kama wewe uma samahani au una maswali kuhusu majeraha yaliyotokana na kuwa kwako katika utafiti, tafadhali wasiliana na madaktari katika kliniki ya utafiti. Huduma katika kituo cha afya yake yamani kwa wazi kwako wewe wana ujuzi wa majeraha, unaweza kujitahili au kucheza kwa muda uleza.

---

kama hilo. Hata hivyo, sio mchunguzi mkuu wala Benki ya Dunia wadhamini wa utafiti huu walio na mpango wa kufidia gharama yako kama wewe utaumia au kuna matokeo mengine mabaya.

**Maswali**
Umeelezewa kuhusu utafiti huu na maswali yako kujibiwa. Kama una maswali mengine yoyote kuhusu haki zako, KWA HABARI AU MASWALI KUHUSU HAKI ZAKO KAMA MSHIRIKI KWENYE UTAFITI UNAWEZA KUWASILIANA NA: WACHUNGUZI WAKUU: Daktari Willie Githui wa KEMRI, Kituo cha Utafiti wa Magonjwa ya Kupumua, S.L.P. 47855 00100 - Nairobi, nambari ya simu: +254 710 492533, barua pepe: wgitthui@yahoo.com au wakaguzi washirika, Daktari Thomas Ogaro, nambari ya simu: 254 722 77 00 90, barua pepe: thomasogaro @ yahoo.com

**Maelezo rasmi ya mawasiliano** kwa ajili ya maswali kuhusu: masuala ya haki i) kwa ushiriki wa washiriki ii) majeraha yanayohusiana na utafiti; na iii) utafiti wenyewe, wasiliana na Katibu Mkuu, KEMRI /Kamati ya Maadili ya Kitaifa, S.L.P 54840 00200, Nairobi. Simu 020 272 2541, 0722 205901; 0733 400003

**Kujiunga kwa hiari yako mwenyewe**
USHIRIKI KATIKA UTAFITI NI WA HIARI. Una haki ya kukataa kushiriki au kujiondoa katika hatua yoyote kwenye utafiti huu bila ya adhabu au kupotea kwa faida ambazo una haki kupata.

**Sahihi yako au alama ya kidole gumba zinamaanisha nini**
Sahihi yako au alama ya kidole gumba hapa chini ina maana kwamba unaelewa taarifa uliyopewa kuhusu kushiriki kwako katika utafiti na katika fomu hii ya kuomba idhini. Ikiwa unataka kushiriki katika utafiti huu, inakubidi kutia sahihi au kuweka alama ya kidole gumba hapa chini.
FOMU YA KUOMBA IDHINI YA KUCHUKUA SAMPULI

Huu mradi unaotarajia kujunga nao ni wa kutusaidia kuamua chaguo bora la vipimo vya uchunguzi wa kifua kikuu litakalo wezesha kugunduliwa mapema kwa kifua kikuu na kufanya uamuzi kuhusu matibabu. Ikiwa utakubali kushiriki kwene na utafiti huu, utaombwa kujaza dodoso, kuchukuliwa makohozi na kupima hali yakani ya virusi vya ukimwi.


Uko huru kujitaa au kutojibu maswali yoyote wowote bila matokeo yoyote. Ikiwa utakubali kushiriki kwene na utafiti huu, tafadhali weka sahihi hapa chini, onyesha kuwa umesoma na kuelewa asili ya utafiti huu na majukumu yako kama mshiriki na utafiti, usumbufu unaohusiana na kushiriki kwa hiari kwene na utafiti na kwamba maswali yako yote na wasiwasi unaohusiana na utafiti huu yamejibiwa kikamilifu. Utapokea nakala ya hati ya kuomba idhini iliyooneka sahihi uondo nayo.

Sahihi ya Mshiriki wa utafiti na tarehe

Alama ya kidole gumba cha mshiriki wa utafiti na tarehe

Sahihi ya mwenye kuchukua idhini na tarehe

Sahihi ya shahidi na tarehe