2. SPECIFIC AIMS

Although targets for global tuberculosis (**TB**) control call for a 50% reduction in incidence by 2025[1], TB incidence worldwide is falling by only 2% per year.[2] A primary reason is that in high burden countries treatment of patients with diagnosable TB is consistently delayed, leading to continued TB transmission. Standard TB evaluation practices do not prioritize early diagnosis or treatment. Community health centers take multiple days to collect sputum from patients for microscopic examination and the multiple visits are inconvenient and costly for patients.[3-7] Consequently, many patients are lost before TB can be diagnosed or treated. In addition, microscopy has poor sensitivity. Although a semi-automated molecular test (Xpert MTB/RIF [**Xpert**]) that identifies 90% of TB cases within 2 hours is now available to address these barriers and has been recommended as the initial diagnostic test for pulmonary TB[8], it cannot be deployed at most peripheral health centers in low-income countries because of cost and infrastructure requirements.[9] To achieve meaningful progress towards TB elimination, there is an *urgent need* to deliver TB microscopy services in a streamlined manner that both enables same-day treatment of the most infectious (*i.e.,* smear-positive) TB cases and facilitates access to and utilization of Xpert, even when it is not available at the point-of-care.

Our *long-term goal* is to disseminate patient-centered approaches to TB diagnosis in high burden countries. The *overall objective* of this proposal is to assess the effectiveness, implementation and costs of a streamlined, single-sample (**SIMPLE)** TB diagnostic evaluation strategy. The components of the SIMPLE TB strategy were selected based on both a theory-informed assessment of barriers to TB diagnostic evaluation at community health centers in Uganda and a process of engagement with local stakeholders. The components include: 1) Single-sample LED fluorescence microscopy (**LED FM**); 2) Daily transport of smear-negative sputum samples to Xpert testing sites; 3) SMS-based reporting of Xpert test results to patients and health centers; and 4) Routine feedback of TB evaluation metrics to health center staff. Our central hypothesis is that the SIMPLE TB strategy will increase the number of patients with active TB for whom treatment is initiated. This hypothesis is based on our own preliminary data that each component is feasible and improves process metrics that reflect high quality TB diagnostic services.

To test our central hypothesis, we will conduct a *pragmatic cluster-randomized trial* at community health centers that provide TB microscopy services in Uganda, where we have a strong partnership with the National TB Program (**NTP**) and an established research infrastructure. We propose an *effectiveness-implementation hybrid design* in which, concurrent with the clinical trial, we will evaluate the implementation of the multi-faceted strategy across study sites using both quantitative and qualitative methods. We will use the RE-AIM framework to evaluate how our strategy affects processes and outcomes important to patients and TB programs, and to determine its scale-up potential. RE-AIM encompasses 5 dimensions common to successful multi-level interventions: depth of reach into a target population; effectiveness; factors that promote adoption; resources needed for implementation; and factors that ensure maintenance over time.[10] Our specific aims are:

Aim 1: To compare the yields of standard and SIMPLE TB diagnostic evaluation strategies. We will randomize 20 community health centers to continue standard TB evaluation (routine LED FM plus referral of selected patients for Xpert testing per existing processes of care) or to implement the SIMPLE TB strategy. We will compare reach and effectiveness based on the numbers and proportions of patients (N=6800) who complete TB testing, are found to have TB, and have treatment initiated within one week (**Figure 2**).

Aim 2: To identify processes and contextual factors that influence the effectiveness and fidelity of the SIMPLE TB strategy. We will use quantitative process metrics to assess the adoption and maintenance over time of the core components of the SIMPLE TB strategy. We will also collect quantitative and qualitative data to describe the fidelity of implementation of each component and faithfulness to our conceptual model.

Aim 3: To compare the costs and epidemiological impact of standard and SIMPLE TB diagnostic evaluation strategies. We will model the incremental costs and cost-effectiveness of SIMPLE TB relative to standard TB diagnostic evaluation from the health system and patient perspective. We will then construct an epidemic model of the population-level impact of the SIMPLE TB strategy on TB incidence and mortality.

We anticipate that completion of these aims will provide a comprehensive assessment of the comparative effectiveness, implementation and population-level impact of a patient-centered approach to TB diagnostic evaluation. These outcomes will have an important positive impact because >50 million people worldwide initiate TB diagnostic evaluation at community health centers annually.[11] If successful, the proposed studies will lead to progress towards TB elimination by strengthening health systems and reducing the cost and burden of TB diagnostic evaluation for patients, thereby ensuring that more people with TB are diagnosed and treated.

3. RESEARCH STRATEGY

3.1 SIGNIFICANCE

Prompt diagnosis and treatment of TB patients is essential to making progress towards TB elimination. However, at least 3 million of the estimated 9 million new cases in 2013 were not detected and reported to the World Health Organization (**WHO**).[2] There are three overarching reasons for this large gap: TB patients are not being notified to public health authorities, not seeking care, or not being diagnosed and treated even after seeking care. The last reason represents a clear health system failure that is pervasive in high burden countries – a recent systematic review of published studies found that up to 38% of sputum smear-positive patients in Africa and 28% in Asia are lost to follow-up prior to treatment initiation.[12] Patients with smear-negative TB are even less likely to complete the diagnostic cascade of care and be linked to treatment.

A principal reason for these failures in linkage to care is the inadequacy of the current approach to TB diagnosis at community health centers. It is well known that sputum smear microscopy, the most common test for TB at community health centers worldwide, has important limitations that contribute to delays in TB diagnosis and treatment. First, smear microcopy has sub-optimal sensitivity, identifying only about 50% of patients who actually have TB.[13] Second, the typical process of sputum collection and smear examination is burdensome for patients. Patients are usually asked to submit a sputum specimen on the day of presentation, return the following morning to submit a second specimen, and return a third time for treatment initiation (if smear-positive) or to consider further workup (if smear-negative). For already poor patients in high burden countries, the direct and indirect costs of this standard multi-day diagnostic evaluation process consume up to 3 months of household income[3-7]. It is therefore not surprising that a substantial proportion do not return after their initial health center visit to submit additional sputum specimens, collect results or initiate treatment if smear-positive.[14-17] In addition, when sputum smears are negative, our prior studies in Uganda suggest that <20% of patients are willing to spend additional money to travel to a district hospital for further testing.[6]

To address these limitations, there has been substantial donor investment in scale-up of Xpert MTB/RIF (**Xpert**)[18], a novel semi-automated molecular assay endorsed by the WHO in 2010 and by the US FDA in 2013. Xpert identifies 90% of TB cases, has a 2-hour turn-around time, and can be performed with minimal training and human resource requirements.[19] Although this represents an important advance, modeling analyses indicate that Xpert is unlikely to bend the TB incidence curve significantly, primarily because it cannot be deployed at community health centers in high burden countries.[20] Indeed, because of high device costs and infrastructure requirements, the vast majority of Xpert devices are being placed at district or higher-level facilities[18] (for example, 44 of 58 devices currently in Uganda), which are accessed by <15% of the population.[21] Many countries have therefore adopted a hub-and-spoke model in which several community health centers (spokes) are linked to an Xpert testing site (hub). However, a cluster-randomized trial has found that Xpert implementation using a hub-and-spoke model did not impact mortality; the major reason was failure to link patients with confirmed TB to treatment.[22] Thus, strategies for successful referrals from community health centers to health facilities in which Xpert and similar tests can be deployed are essential to achieve access, utilization and impact on patient and public health outcomes.

Our contribution here will be to provide definitive evidence of the effectiveness, implementation and impact of an innovative, theory-informed strategy to streamline TB diagnostic evaluation at community health centers. *This contribution is significant because it is expected to help identify and initiate therapy for most patients with active pulmonary TB who present for care.* The SIMPLE TB strategy addresses key barriers to TB diagnostic evaluation (see Section 3.3.2). We propose to restructure clinic-level procedures (*i.e.,* single-sample LED FM) to address key pre-disposing factors: the inconvenience and high financial burden of TB diagnostic evaluation on patients and low provider self-efficacy related to identifying and treating smear-positive patients. We further propose daily sputum transport and SMS-based results reporting as relatively low-cost health systems interventions to enable patient access to Xpert testing and linkage to treatment in a timely manner. Last, we propose performance feedback using indicators derived from routinely collected data as a low-cost strategy to reinforce and maintain delivery of high quality TB diagnostic evaluation services. We have sufficient preliminary data to suggest that each component of the SIMPLE TB strategy is feasible and effective in closing the linkage-to-care gap (see Section 3.3.2). High-quality evidence is now needed to guide TB policy makers in deciding whether to adopt the SIMPLE TB strategy, and on how best to implement it at other health centers.

The proposed studies embody the DIRH RFA's goal to improve the quality of health, delivery of services and the utilization and sustainability of evidence-based tools and approaches. Single-sample microscopy itself requires no new technology or trained staff. It is the simplest proven adaptation around which to reorganize clinic-level procedures to enable same-day diagnosis and treatment of smear-positive TB patients and referral of smear-

negative samples for Xpert testing at higher levels of care in accordance with national and international guidelines.[8, 23] It places the perspective of patients first, and reorganizes healthcare systems in a manner that may have ancillary benefits for managing other conditions for which same-day results are often critical for linkage to care. Together, the components of the SIMPLE TB strategy can be expected to maximize the gains in sensitivity achieved with novel TB diagnostics such as Xpert, even when not deployed at the point-of-care. Relying solely on novel diagnostic technologies without also supporting health system interventions to facilitate their uptake and use is unlikely to result in sustained and meaningful progress in the ongoing fight against TB.

3.2 INNOVATION

Innovative intervention. Large-scale expansion of novel molecular diagnostics to community health centers is unlikely given limited external donor funding and the existing shortfalls in National TB Program budgets (>$2 billion for 2014-2015).[2] Thus, the SIMPLE TB strategy represents an innovative approach to enhancing access to and use of novel TB diagnostics. Instead of relying solely on the technology itself to achieve point-of-care access, the SIMPLE TB strategy strengthens existing referral networks through a combination of behavior change and mHealth-based interventions that are feasible within the local context. To our knowledge, no previous studies have adopted a theory-informed approach to improve the quality of TB diagnostic evaluation and improve linkage-to-care at community health centers in high TB burden countries.

Innovative perspective. Interventions that do not work for patients will not have a desirable public health impact. We highlight this perspective through a package of interventions that are likely to make TB diagnostic evaluation more convenient and less costly for patients (*i.e.,* patient-centered). At the same time, the SIMPLE TB strategy targets key barriers to delivery of high-quality TB diagnostic services cited by front-line health workers (see Section 3.3.2). We believe a perspective that emphasizes overcoming patient- and provider-level barriers is critical for increasing diagnosis and treatment of TB at community health centers.

Innovative analysis. We will use a variety of analytic techniques, from quantitative clinical research to qualitative behavioral science to epidemic modeling, in order to evaluate the SIMPLE TB strategy at every level, from operational processes to population-level impact. Our use of the RE-AIM framework provides a comprehensive structure for our multi-level analytic approach.[10]

Innovative outcomes. We have designed this proposal not only to evaluate the effectiveness of a specific package of customized interventions (*i.e.,* the SIMPLE TB strategy) but also to describe in detail 1) the process by which the SIMPLE TB strategy may or may not lead to improved individual- and population-level outcomes and 2) the factors that influence its adoption and adaptation at study sites.

3.3 APPROACH

3.3.1 Overview. Building on the work of a prior R21 (AI096158, PI Cattamanchi), we now propose a pragmatic cluster-randomized trial to comprehensively compare the SIMPLE TB strategy to standard TB diagnostic evaluation for each of the key processes following TB symptom screening including testing, diagnosis and treatment initiation. We will use the RE-AIM framework to answer three central questions:

- **Comparative Effectiveness:** Can a theory-derived intervention (SIMPLE TB strategy) improve TB diagnosis and treatment initiation rates relative to the prevailing standard-of-care? (Aim 1)
- **Implementation Science:** What are the “bottlenecks” that affect the uptake, adoption and impact of the SIMPLE TB strategy at routine health centers in high burden countries? (Aim 2)
- **Impact and Cost-Effectiveness:** What is the likely population-level impact and cost-effectiveness of streamlined TB diagnostic evaluation based on the SIMPLE TB strategy? (Aim 3)

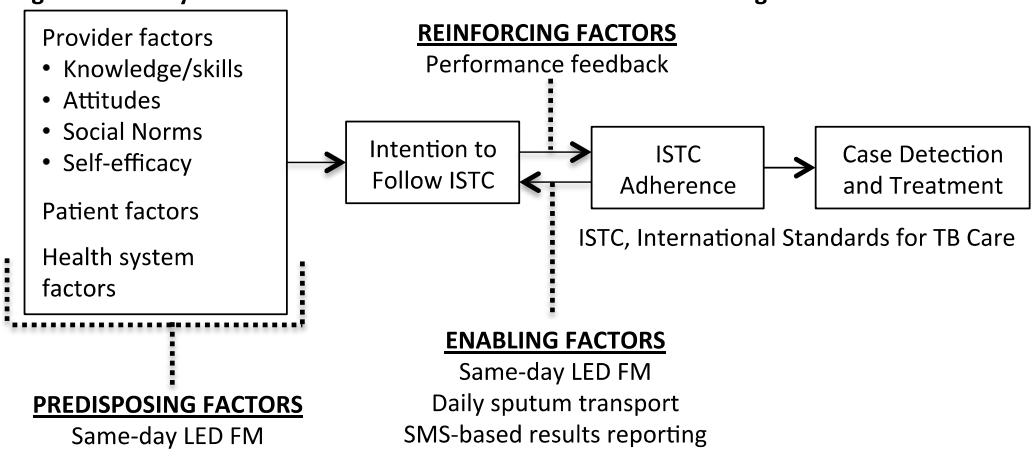
Our proposed studies will address these aims conceptually, not chronologically, and will run concurrently. In Aim 1, we will conduct a cluster-randomized trial to probe the reach and effectiveness of the two strategies, using routine programmatic data to follow patients through each of the key TB diagnostic evaluation processes and outcomes. In Aim 2, we will use quantitative and qualitative methods to measure the adoption, implementation, and maintenance of the SIMPLE TB strategy at community health centers. In Aim 3, we will use empirical costing, economic evaluation, and mathematical modeling to compare the two strategies in terms of their cost-effectiveness and epidemiological impact on TB incidence and mortality to inform policy development and scale-up in other settings.

3.3.2 Justification, Feasibility and Preliminary Data

Failures in linkage to appropriate TB care. Our team has considerable experience working at community health centers in Uganda. In 2008, **Drs. Cattamanchi**, **Katamba** and **Davis** established the Uganda TB Surveillance Project (**UTBSP**) at six rural health centers dispersed throughout the country. We used data collected on all patients who presented to the six health centers to quantify gaps along the cascade of care for patients referred for TB diagnostic evaluation.[15] We found that 27% of patients referred for sputum smear examination failed to complete testing and 29% of smear-positive patients did not initiate treatment. In addition, we found that clinicians rarely referred smear-negative patients to the district hospital for additional evaluation or testing. These data highlight the need for strategies to close gaps in the TB diagnosis cascade of care.

Theory-informed intervention design. **Drs. Cattamanchi, Katamba**, **Handley** and **Ackerman** conducted a mixed methods study at the six UTBSP health centers to better understand reasons for gaps along the TB diagnosis cascade of care and inform intervention design. We conducted semi-structured interviews with providers to elicit their perceptions regarding barriers to delivery of high-quality TB diagnostic services (*i.e.,* ensuring patients referred for TB evaluation are linked to recommended care) and administered surveys to patients undergoing TB diagnostic evaluation to characterize pathways and costs associated with obtaining a TB diagnosis. To guide the process, we employed the Theory of Planned Behavior as the conceptual framework and the PRECEDE model to select intervention components (**Figure 1**). In a systematic review of guideline implementation studies, the Theory of Planned Behavior was the most likely theory to predict guideline adherence.[24] This theory asserts that intention is the best predictor of behavior and that three factors mediate the strength of intention: (1) attitudes (expected value of behavioral performance); (2) subjective norms (what important others think about the behavior); and (3) self-efficacy (perception of ability to overcome barriers to behavioral performance).[25] We chose the PRECEDE model based on its strong empirical base and applicability to guideline adherence. The model is based on three factors relevant to health behavior change: (1) *predisposing* factors – prior motives that either support or inhibit behavior; (2) *reinforcing* factors – rewards or punishments following a behavior or anticipated as a consequence of it; and (3) *enabling* factors – objective characteristics of an individual or environment that facilitate behavior.[26] A meta-analysis of 50 randomized controlled trials of continuing medical education demonstrated that the studies employing a combination of interventions representing PRECEDE categories were the most likely to influence patient outcomes.[27]

Figure 1. Theory-informed barrier assessment and intervention design.



1) Barriers to TB evaluation – Providers: We conducted structured interviews with 22 staff at the six UTBSP health centers between February and November 2011.[28] Interviews were transcribed, coded with a standardized framework, and analyzed to identify emergent themes. Key findings are shown in **Table 1**.

Table 1. Key provider-level barriers to high-quality TB evaluation.

PRECEDE framework	Recurring themes highlighting barriers targeted by the SIMPLE TB strategy
Predisposing factors (Knowledge, attitudes, beliefs, intention)	• Time and resource constraints → low self-efficacy • Low motivation of staff
Enabling Factors (Factors that if addressed make it easier to initiate the desired behavior)	• Failure of patients to return after initial visit • Inability to track and follow-up patients → low-self-efficacy *"When they have a cough for more than 2 weeks they are sent to the lab. But the problem is they get the first sample and sometimes, actually most times they don't bring the second sample."*

Reinforcing Factors (Factors that if addressed make it easier to continue the desired behavior)	• Lack of communication and coordination among staff • Insufficient oversight from NTP *"…Actually at times we have met but we don't meet [regularly], only when we realize there is a problem that's when we communicate and say why is this happening, then we try to rectify."*

3) Intervention selection: We designed the SIMPLE TB strategy in consultation with the Uganda NTP (**see Letter of Support, Frank Mugabe**) to target modifiable clinic-level barriers identified in our formative assessment as well as key theoretical constructs (**Figure 1**). Re-structuring clinic-level procedures via single-sample LED FM was selected to reduce laboratory workload and reduce the burden of sputum smear evaluation on patients and providers, thereby increasing provider self-efficacy and enabling linkage of smear-positive patients to treatment. Daily sputum transport and SMS-based results reporting were selected to enable linkage of smear-negative patients to the ongoing scale-up of Xpert testing at more central facilities. Finally, behavioral theories indicate that performance feedback makes providers aware when current practices are inconsistent with those of peers or guidelines, changes beliefs about the consequences of current practices, social norms and perceived ability to perform the desired behavior.[29] Thus, performance feedback was selected because it complements the other intervention components in reinforcing adherence to TB evaluation guidelines.

Pilot data on SIMPLE TB strategy components.

1) Same-day microscopy and single-sample LED FM: In a systematic review of over 7000 patients, **Drs. Cattamanchi** and **Davis** showed that there was no difference in the pooled sensitivity (64% vs. 63%, p=0.71) of front-loaded (two-specimens collected one hour apart) vs. standard (two specimens collected over two days) sputum smear microscopy.[30] Based on these findings, the WHO endorsed "same-day" microscopy services in 2010 and in addition endorsed LED FM as a strategy to increase sensitivity and reduce laboratory workload relative to light microscopy.[23, 31] **Drs. Cattamanchi, Davis and Katamba** have since shown that same-day LED FM can be implemented successfully as a replacement for conventional light microscopy at the six UTBSP health centers.[32] Following a five-day training at each health center, there were no major quantification errors during routine external quality assurance monitoring. In addition, following implementation of LED FM in a stepped-wedge fashion, the proportion of patients who completed sputum smear evaluation across the 6 health centers increased from 77% to 96% (p<0.001), and 97% of smear-positive patients initiated treatment. Finally, **Drs. Cattamanchi** and **Davis** showed that the accuracy of single-sample LED FM (one sample, two smears) was non-inferior to that of conventional LED FM (two samples over two days with one smear from each sample)[33], establishing it as an adaptation to facilitate delivery of same-day microscopy services.

*2) Sputum transport for Xpert testing***:** As part of an R21-funded (AI10603, PI Dowdy) study, **Drs. Dowdy**, **Cattamanchi, Katamba** and **Davis** are characterizing Xpert implementation in Uganda. Similar to many other high burden countries, Uganda has chosen to adopt a hub-and-spoke model in which an Xpert testing site (typically a district hospital or district health center) is connected with 5-10 community health centers. 35 such Xpert referral networks have been established to date, of which 8 are awaiting installation of the Xpert device at the hub and 6 are awaiting procurement of Xpert devices. Thus, we anticipate 175-350 community health centers will be available to screen for eligibility for the proposed clinical trial. Per Uganda NTLP guidelines, community health centers are instructed to refer samples from patients with HIV-infection, children <15 years old and patients with risk factors for drug resistance for Xpert testing. Sputum samples are picked up via motorbike every 1-2 weeks from each health center and results are brought back on the next sample pick-up day (*i.e.,* up to 2 weeks after sputum collection). In reviewing one month of data from 18 health centers, we found that 33% (89/268) of smear-positive patients had not initiated treatment, few samples were sent from each health center to Xpert hubs (median 7/month), and 36% (7/19) of Xpert-positive patients had not initiated treatment. These data highlight the need for augmented systems to support more timely access and utilization of Xpert testing, as well as reporting of results, for all sputum smear-negative patients.

3) Linkage to Xpert testing and results: **Drs. Cattamanchi, Moore, Fielding and Katamba** received a pilot grant from the Wellcome Trust to evaluate the feasibility of linkage to Xpert testing for all smear-negative patients at community health centers in Uganda. To date, we have shown that "boda boda" (local motorbike) drivers could be used to successfully transport sputum samples between 4 health centers and their affiliated Xpert testing hubs on a daily basis. The distance between health centers and Xpert hubs ranged from 20-50 km. In addition, we have developed local experience with the GxAlert software (SystemOne, USA). GxAlert was developed to facilitate automated reporting of Xpert test results to NTPs and has been implemented in at least 8 countries. The software automatically pulls test information from a country's Xpert devices to a national or global server and links to an application that can generate site-specific reports. We facilitated training on installation and use

of the GxAlert software for project and Uganda NTRL staff. In addition, we worked with the software developers and NTRL to 1) include patient and health center mobile phone numbers as part of the information uploaded to the server and 2) configure SMS-based reporting of results to patients and health centers (**see Letter of Support, Moses Joloba**). We installed GxAlert at two Xpert hubs, and both were able to report test results in an automated fashion via server upload to the NTP and via SMS to the referring health center and patients. The research proposed in this R01 application will assess whether support systems can be integrated in such a fashion that SMS-based results reporting, functioning as one part of those systems, can be cost-effective and should be scaled-up in Uganda and beyond.

4) Performance feedback: **Drs. Cattamanchi, Davis, Handley and Katamba** have evaluated the feasibility and impact of performance feedback at the six UTBSP health centers. Performance feedback is a strategy employing regular monitoring and feedback to allow health care workers to critically analyze performance and identify areas for improvement. It has been shown previously to be effective for improving laboratory practices and quality of smear examination.[34] A systematic review of audit and feedback interventions identified 5 factors associated with greater impact: low baseline performance, feedback coming from a supervisor or colleague, feedback provided multiple times, feedback delivered in both verbal and written form, and feedback including explicit targets and an action plan.[29] Thus, our intervention involved delivery of a monthly Report Card which displayed 1) TB evaluation process metrics for the current month and for the previous 6 months and 2) performance data averaged across all six health centers. After staff introduced the Report Card, it was sent electronically each month to the health center in-charge or TB focal person. Health workers were asked to review the Report Card at monthly staff meetings to devise a performance improvement plan. This continued monthly, with each new Report Card being used to evaluate the success of plans developed the previous month and determine the need for new actions. Following implementation of performance feedback in a stepped-wedge fashion, the proportion of patients who received guideline-adherent care increased from 52% to 67% ($p<0.001$) across the 6 UTBSP health centers in a multivariate, hierarchical modeling analysis.[35]

Other relevant experience of study investigators.

1) Diagnostic evaluations and cluster-randomized trials (Aim 1): **Drs. Davis, Katamba and Cattamanchi** have completed protocol development and are initiating enrollment into a cluster-randomized trial of mHealth-based strategies to facilitate household contact investigation of active TB cases in Kampala (R01AI104824, PI Davis). **Dr. Moore** has led field evaluations of diagnostic technologies and strategies for TB for more than a decade[36-42]. **Dr. Fielding** (biostatistician) has over 15 years of experience with design and analysis of randomized controlled trials[43-51], including cluster-randomized trials aiming to reduce the burden of TB in settings of HIV prevalence[52-55] and evaluating the effect of routine implementation of Xpert in South Africa.[22] Last, **Drs. Mugabe and Joloba** provide long-standing programmatic experience in implementing TB control interventions.

2) Implementation science and mixed methods research (Aim 2): In addition to the quantitative and qualitative studies that informed the design of the SIMPLE TB strategy, **Drs. Cattamanchi** and **Handley** used a combination of process metrics, in-depth interviews and focus group discussions to characterize and understand gaps in the pathway to diagnosis of multidrug-resistant TB in Cambodia.[56] **Drs. Handley** and **Ackerman** are leading qualitative data collection and analysis to inform the design and adaptation of the mHealth-based contact investigation strategy for Dr. Davis' R01. In addition to their work on TB, **Drs. Handley and Ackerman** have a long track record of implementation science training and research, and specifically in designing, implementing and evaluating clinic-based interventions used mixed methods approaches.[57-64] They recently received funding through the UCSF Clinical and Translational Sciences Institute to develop a user guide for faculty interested in publishing data from mixed methods studies.

3) Economic evaluation and mathematical modeling (Aim 3): **Dr. Dowdy** has previously conducted numerous economic evaluations of TB diagnostics that have highlighted key operational drivers of cost-effectiveness.[65-68] **Drs. Dowdy** and **Cattamanchi** recently described the unique challenges of economic analyses evaluating scale-up of TB diagnostics (and methods to overcome them)[20], and **Dr. Dowdy** was the senior author of an NIH panel report evaluating opportunities for cost-efficient implementation of diagnostics for HIV and TB.[69] Regarding dynamic mathematical modeling, **Dr. Dowdy,** in collaboration with **Drs. Cattamanchi** and **Davis**, compared the impact of same-day microscopy at community health centers vs. scale-up of Xpert at central health facilities in sub-Saharan Africa.[70] They showed that same-day treatment of smear-positive TB and scaling-up Xpert at central health facilities would each avert half a million TB cases (9-11% reduction in annual TB incidence) over 10 years. But the two combined would lead to a 2-fold greater reduction in TB incidence (29%) and 1.5-fold greater reduction in TB mortality (44%) than either alone. In addition, **Dr. Dowdy** found that implementation strategy and patient referral systems were critical determinants of the population-level impact of Xpert scale-up

in India[71], and that the impact of novel diagnostics depends on closing gaps in the diagnostic care cascade.[72] Thus, if validated in a well-designed clinical trial, our proposed intervention has strong potential to improve patient and public health outcomes.

3.3.3 Research Design and Methods

Aim 1. To compare the yields of standard and SIMPLE TB diagnostic evaluation strategies.

Introduction. The *rationale* for this aim is that high quality evidence that the SIMPLE TB strategy improves TB evaluation outcomes at routine health centers is needed to drive policy and scale-up. The *objective* is to determine the comparative effectiveness of the SIMPLE TB strategy relative to standard TB diagnostic evaluation. Our *scientific approach* will be to conduct a cluster-randomized trial at 20 community health centers in Uganda. Health centers will be randomly assigned to either standard-of-care or intervention (SIMPLE TB strategy) arms (10 clusters per arm). Study teams will complete quarterly site visits to collect outcome data from existing TB laboratory and treatment registers at the health centers and their affiliated district/provincial hospital (*i.e.,* Xpert testing site) for 340 consecutive patients referred for TB diagnostic evaluation at each study site (N=6800 total patients). We will compare the two strategies using several metrics for each of the key processes and outcomes of TB diagnostic evaluation, which we have also mapped to their associated RE-AIM dimensions (**Figure 2**). Specifically we will compare the 1) absolute numbers of patients completing each step of the TB diagnostic evaluation process (a measure of public health *yield*); 2) proportions completing each step (a measure of the *efficiency* of TB evaluation for individuals and/or health systems); and 3) time to complete each step (a component of the potential impact of these strategies on transmission). Our *working hypothesis* is that the SIMPLE TB strategy will improve the yield, efficiency, and impact of TB evaluation at each key step from referral of patients for sputum examination to treatment initiation, as compared to standard TB diagnostic evaluation. *Expected outcomes* include detailed, multi-level metrics of the RE-AIM reach and effectiveness dimensions of these strategies. The *expected impact* of our findings will be to provide evidence-based guidance for decision-making by clinicians, patients, and policymakers on the overall return of these strategies, and to deliver key inputs for the cost-effectiveness and transmission modeling activities in Aim 3.

Figure 2. Key clinical processes, study metrics, and RE-AIM dimensions

Key TB Evaluation Processes & Outcomes

Testing → Diagnosis → Treatment

Research Metrics	RE-AIM Dimensions			
	Reach	*Reach*	*Effectiveness*	*Effectiveness*
Yield	Number referred for smear examination	Number referred for Xpert testing	Number testing positive by 1) smear & 2) Xpert	Number treated for TB
Efficiency	Proportion completing smear examination	Proportion completing Xpert testing	Proportion testing positive by 1) smear & 2) Xpert	Proportion treated for TB
Speed	Time to complete smear examination	Time to complete Xpert testing	Time to diagnose TB by 1) smear & 2) Xpert	Time to treat for TB

Design. We propose a pragmatic, parallel cluster-randomized trial design. The unit of randomization will be health centers (N=20). The unit of analysis will be individuals undergoing TB diagnostic evaluation (N=6800).

Interventions. The conventional (standard-of-care) approach to TB diagnostic evaluation at community health centers involves collection of a spot specimen at the initial patient visit and an early morning specimen at the second patient visit. Technicians prepare one smear from each specimen and examine the stained smear under a microscope. Consultation for results and treatment initiation generally require additional patient visits. In Uganda, NTP policy specifies that sputum from selected patients (HIV-infected, suspected drug resistance) should be referred for Xpert testing. However, uptake of this policy is sporadic and sputum transport to Xpert testing sites occurs at most on a weekly basis, with results returned to health centers the following week.

The standard-of-care strategy will be compared to the multi-faceted SIMPLE TB strategy that engages both laboratory and clinical services at community health centers to enable diagnosis and treatment of patients with smear-positive TB and referral of samples from smear-negative patients for further testing at the first visit. Specifically, the intervention will include the following core components (see section 3.3.2 for details): 1) Single-sample LED fluorescence microscopy (**FM**); 2) Daily transport of sputum specimens to an affiliated Xpert testing site; 3) SMS-based reporting of Xpert results to health centers and patients; and 4) Quarterly report card summarizing TB diagnostic evaluation quality indicators. Briefly, sites randomized to the intervention arm will incorporate the following: 1) Lab-based algorithms to prepare and examine two smears from a single sputum specimen within two hours of specimen collection; 2) Integration of laboratory, clinical, and on-site pharmacy

services to ensure that smear-positive patients start treatment before leaving the clinic and smear-negative patients (as well as patients with HIV or risk factors for drug-resistant TB) have their sputum sample transported to an affiliated Xpert testing site; 3) SMS-based reporting of Xpert results to health centers and patients to enable treatment initiation, if indicated, in at most one additional clinical encounter; and 4) Performance feedback of TB diagnostic evaluation quality indicators to facilitate continuous quality improvement. Of note, patients will continue to have the option of returning to provide an early morning sputum specimen for smear microscopy as per the routine procedure.

Target setting and population. The target setting is community health centers with TB microscopy units (*i.e.,* the lowest level of the health system where TB diagnostic services are provided by the Uganda NTLP). We will include community health centers that 1) Use standard (multi-day) sputum smear microscopy as the primary method of TB diagnosis; 2) Participate in NTP-sponsored external quality assurance (EQA) for sputum smear microscopy; 3) Are affiliated with a district or regional hospital that offers Xpert testing; and 4) Agree to be randomized to standard-of-care vs. intervention arms. We will exclude community health centers that: 1) Perform sputum smear examination on <200 patients per year or 2) Diagnose <20 smear-positive TB cases per year.

We will compare the standard-of-care and intervention strategies using data on consecutive adults who have sputum collected for TB diagnosis at participating health centers during the trial period. We will exclude data on patients with TB undergoing sputum smear evaluation for monitoring of response to anti-TB therapy.

Sampling and recruitment. We will work with the Uganda NTLP to select representative urban and rural community health centers from among the 175-350 that are linked to Xpert hubs and meet eligibility criteria.

Procedures and measurements.

1) Site preparation – In Year 1, we will standardize key operational and technical aspects of routine TB diagnostic evaluation across all study sites. Specifically we will: **A)** Provide TB diagnostic evaluation guideline training to health workers using interactive training materials[15]; **B)** Implement routine cough screening of all patents or provide refresher training at sites already performing routine cough screening in accordance with WHO and Uganda TB infection control guidelines[73]; and **C)** Implement LED FM or provide refresher LED FM training at sites already using LED FM using an established protocol.[32]

2) Randomization – In Year 2, we will randomly allocate health centers to either continue standard-of-care TB diagnostic evaluation or implement the SIMPLE TB strategy using stratified randomization with restriction. Health centers will be grouped into two strata using baseline data for the primary outcome (see Data Collection below), and randomized within strata to help reduce between-cluster variation and improve balance between arms at baseline.[74] Restriction, a common approach in cluster-randomized trials with a small number of clusters, will be used to help achieve baseline balance of important site- and patient-level covariates.[75] We will consider restricting on factors likely to be associated with the primary outcome including health center region (four quadrants of Uganda), health center size (based on volume of patients tested for TB), HIV prevalence among TB patients, and patient cost and satisfaction with care. The restriction factor will be calculated and the validity of the restriction assessed using the validity matrix.[76] The Trial Statistician (KF) will be responsible for the randomization, which will be conducted in the presence of representatives from the Uganda NTLP and participating health centers.

3) Intervention introduction – Following randomization, we will conduct a 2-day site visit to each intervention and control health center. *At intervention health centers*, we will engage staff in a discussion of the site-specific laboratory, clinical, and pharmacy workflow reorientation required as part of the SIMPLE TB strategy. GxAlert software will also be installed and staff trained at affiliated Xpert testing sites. The software will be configured to report all test results to the Uganda NTLP via server upload but text messaging of results will be enabled only for samples received from intervention health centers. Study staff will record any immediate adaptations of intervention components. *At control health centers*, we will re-emphasize messages related to cough screening, sputum collection, and TB guidelines presented during the site preparation visit in Year 1.

4) Data Collection – Data collection will begin at least 3 months prior to randomization for the baseline characterization of each study site and continue on a quarterly basis for the trial duration. Study staff will extract patient-level demographic and outcome data from the following sources at each study site: 1) NTLP Laboratory and Treatment registers; 2) Sputum smear and Xpert laboratory requisition forms; and 3) GxAlert software (at affiliated Xpert testing site). Patient-level data will include age, gender, smear results, reason for Xpert referral, Xpert results, and TB treatment status, along with dates for relevant variables. Standardized data collection forms will be created, and research staff will be trained on how to complete the forms.

5) Data Management – Dr. Fielding (statistician) will oversee data management in conjunction with UCSF- and Uganda-based study coordinators using the NIH-recommended Research Electronic Data Capture (RedCAP) software. All data collection forms will be entered into REDCap, with validation of data using range and consistency checks. Quality control procedures will include review of all study data collection forms for completeness and accuracy prior to data capture. The UCSF study coordinator will visit Uganda 2-3 times a year and review a random sample of forms and primary data sources for quality assurance. Queries performed on the database that generate errors will be reviewed, verified and corrected on a monthly basis.

Outcomes and Analyses. Study outcomes across the reach and effectiveness dimensions of the RE-AIM framework are specified in **Figure 2**. The metric designated as the primary research outcome will be the efficiency of completing TB evaluation, specifically the proportion of all patients referred for TB evaluation who initiate treatment for active TB within one week of initial sputum submission. We focus on all patients who initiate treatment for active TB and not just those with confirmed TB (*i.e.,* positive smear or Xpert) for the following reasons. First, we expect that empiric treatment will be similar across the two study arms. Second, failure to include empiric treatment could bias results in favor of the intervention arm if patients who complete referrals for Xpert testing and are found to be Xpert-positive would have been started on TB treatment regardless.[20,77] Third, patients treated empirically are still reported as TB cases in accordance with WHO guidelines. Thus, the primary outcome is all patients treated for TB. Secondary outcomes include the number and proportion of microbiologically-confirmed (*i.e.,* smear- or Xpert-positive) TB patients initiating treatment as shown in **Figure 2**.

We will calculate and compare all outcomes for the two trial arms using an intention-to-treat analysis. We will use descriptive statistics and 95% confidence intervals to summarize the yield, efficiency, and speed outcomes for the two intervention arms by site. To assess the intervention effect on outcomes, we will use methods appropriate for randomization of a small number of clusters and accounting for the stratified design.[74] A cluster-level analysis, giving each cluster equal weight, will be conducted to calculate unadjusted ratio and difference effect measures, and their associated 95% confidence intervals. Adjusted effect estimates will also be calculated taking into account any imbalance of important factors at baseline by study arm. Pre-specified subgroup analyses (gender and HIV status) will be conducted for the primary outcome. A detailed statistical analysis plan will document methods used for the analysis of primary and secondary outcomes.

k	Absolute effect size
0.2	4.5%
0.25	5.5%
0.3	6.6%

Sample size and power estimates. The study is based on the health clinic being the unit of randomization and aims to demonstrate the superiority of the intervention arm. The sample size calculation uses formulae appropriate for cluster-randomized trials with a parallel design and stratified randomization.[74] The outcome is the proportion of clinic attendees undergoing TB evaluation who have started TB treatment within one week of initial sputum submission. A type I error of 5% and power of 90% is assumed. Data from 6 potential trial sites in Uganda suggest that the average proportion of patients referred for TB evaluation who initiate treatment for active TB within one week (primary outcome) is 9%, and the coefficient of variation (k) between clusters is 0.17. Based on the above assumptions and assuming a k of 0.2, a sample size of 20 health centers (clusters; 10 per arm), and 340 patients per health center, we will have 90% power to detect a 4.5% or greater absolute increase in the outcome proportion in the intervention arm (see Table). The Table also shows detectable absolute effect sizes with power of 90% and larger coefficients of variation. We believe that an absolute increase in TB treatment initiation of 4.5-6.6% is the minimum required for the SIMPLE TB strategy to effect policy change and population-level impact.

Potential problems and alternative strategies. Potential problems include that health centers may not accept to be randomized to intervention vs. control arms and that the assumptions driving our sample size calculation are inaccurate. To mitigate concerns about trial acceptability, health centers in the control arm will receive TB diagnostic evaluation guideline training and refresher microscopy training, both of which are valued by health center staff based on our conversations with local stakeholders including Uganda NTLP representatives and health center in-charges. Nonetheless, should problems arise, we will consider modifying the design from a parallel to a stepped-wedge cluster-randomized trial in which all health centers receive the intervention prior to the end of the trial.[78] Similarly, if baseline (pre-randomization) data indicates our assumptions were inaccurate, we will revise sample size calculations. Both decisions will be made with guidance from a Trial Steering Committee (see Human Subjects section, Data and Safety Monitoring Plan).

Aim 2. To identify processes and contextual factors that explain the effectiveness and fidelity of the SIMPLE TB strategy.

Introduction. A fundamental aspect of implementation research is developing generalizable knowledge

about human and technical aspects of implementation that determine the success or failure of interventions. The relative lack of such knowledge constitutes a major barrier to implementation and dissemination of evidence-based interventions. The objective of this aim is to understand reasons for the success or failure of the intervention. Our rationale and hypothesis is that examining the patterns of **adoption, implementation and maintenance** of the core components of the intervention will provide insights into how to better achieve the desired outcomes. Furthermore, examining the fidelity and local adaptation of these components across sites will facilitate plans for scale-up and adoption in similar settings. Our scientific approach will be to employ both quantitative and qualitative methods to identify important explanatory factors underlying the success or failure of the intervention components. The expected impact will be to advance our knowledge of whether the SIMPLE TB strategy and each of its core components are effective in overcoming bottlenecks to TB evaluation and faithful to the conceptual model (**Figure 1**) we proposed for improving the quality of TB diagnostic evaluation.

Design. Approaches that employ mixed methods are most suitable to those in which the quantitative approach or the qualitative approach, by itself, is inadequate to develop multiple perspectives and a complete understanding about a research problem or question.[79-82] Here, we anticipate that qualitative data will provide a greater depth of understanding of quantitative outcome measures. As such, we propose an explanatory sequential mixed methods design in which quantitative analyses are followed by qualitative analyses to maximize our understanding of the adoption, implementation and maintenance of the SIMPLE TB strategy.[80, 81] As shown in **Table 2**, quantitative data will include detailed process metrics and surveys, and qualitative data will include focus groups and in depth interviews with front-line health workers.

Table 2. Mixed methods evaluation strategy, sample, goal, data collection timing and analysis.

Strategy	Sample	Goal	Data collection	Analysis
Process metrics	All patients referred for TB diagnostic evaluation at intervention sites	Examine variability in adoption and maintenance of intervention components across sites	Entire post-randomization period	Multivariate regression models
Surveys	1) Health workers involved in TB evaluation at all sites* 2) 40 patients per site (800 total)**	Examine whether the SIMPLE TB strategy modifies barriers to TB diagnostic evaluation	Once before and once at least 12 months after randomization	Multivariate regression models
Focus groups	Health workers involved in TB evaluation at intervention sites*	Assess fidelity to each intervention component	At least 12 months after randomization	Thematic interpretation
In depth interviews	Purposive: 20-30 health workers at high- and low-performing intervention sites	Understand reasons for variability in uptake and effectiveness of SIMPLE TB strategy	After trial is completed	Thematic interpretation

* Based on prior experience, we anticipate 5-10 staff members will be involved in TB diagnostic services at each health center (50-100 each at intervention and control health centers); ** Patients will be selected randomly within strata based on gender and timing of health center visit (undergoing TB testing vs. completed testing/initiating TB treatment)

Quantitative measurements.

1) Process metrics – We will use data collected routinely during the provision of TB diagnostic services to evaluate process metrics that reflect adoption of each component of the SIMPLE TB strategy (**Table 3**) overall and within key sub-populations (women and HIV-infected).

Table 3. Process metrics of adoption of SIMPLE TB strategy components.

Component	Process Metric	Data Source
Same-day LED FM	• Proportion with two smears examined at initial visit • Proportion starting treatment at first visit if smear-positive	• NTLP Lab & Treatment Registers • NTLP Lab & Treatment Registers
Daily sputum transport	• Proportion of smear-negative samples transported to Xpert testing site on same day	• NTLP Lab Registers
SMS-based results reporting	• Proportion for whom Xpert result was sent by SMS • Proportion for whom Xpert result SMS was received • Proportion starting treatment within 7d if Xpert-positive	• GxAlert software • SMS service provider logs • NTLP Treatment Registers
Performance feedback	• Proportion of reports discussed at staff meetings	• Staff meeting minutes

2) Patient costs and satisfaction with care – We will administer a survey to collect data on direct and indirect costs (time to complete visit, lost wages, etc.) of TB diagnostic evaluation and satisfaction with TB diagnostic services (see **Appendix 1**). The survey will be administered before and at least 12 months after randomization

(20 per health center [400 total] at each time point). Cost data collection will be based on the Tool to Estimate Patient Costs developed by the TB Coalition for Technical Assistance, which we have already adapted and used in Uganda (see Section 3.3.2). Satisfaction with care will be assessed using 18 items taken from the previously validated Patient Satisfaction Questionnaire (PSQ)[83] and adapted to the Ugandan context.[84] The items are constructed with a five-point Likert scale with categories ranging from "strongly disagree" to "strongly agree", and include both positively and negatively worded questions to minimize the potential bias that occurs from clustering of responses to one side of the scale. The questionnaire measures general satisfaction as well as four dimensions of care known to impact satisfaction: 1) Accessibility, availability, and convenience of health services (3 items); 2) Provider interpersonal skills (5 items); 3) Provider technical competence with respect to patient education, examination and counseling (4 items); and 4) Health facility environment, specifically with respect to the cleanliness and space in the waiting area (2 items).

3) Theoretical constructs – We will administer a survey to health workers to collect data on key constructs of the Theory of Planned Behavior (TPB, **Figure 1**): intention, beliefs/attitude, normative beliefs/subjective norms and perceived behavioral control (see **Appendix 2**). The survey was developed using guidelines for TPB surveys.[85] It will be administered before and at least 12 months after randomization at all health centers.

Qualitative data collection. Qualitative assessments are critical to tailoring and successfully disseminating multi-faceted interventions to other practice settings, and for understanding reasons for adoption or non-adoption of interventions.[86] Our team has extensive experience with the conduct and analysis of focus groups and in depth interviews with health workers through completed[28] and ongoing studies (R01AI104824, PI Davis and USAID PEER Health, PI Katamba). Focus groups (one at each intervention health center) and in depth semi-structured interviews will be designed to elicit health worker perspectives on adoption of the SIMPLE TB strategy and its impact on TB diagnostic evaluation processes. General prompts will be used to orient qualitative data descriptively in specified topic areas. Focus groups and interviews will be conducted by trained and experienced staff, audio-recorded, and professionally transcribed.

Data analysis and statistical methods.

1) Descriptive analyses – We will report process metrics on a monthly basis to assess adoption and maintenance of each intervention component overall, within key patient sub-groups, and at individual sites. We will report median and change between pre- and post-randomization assessments in **A)** patient costs; **B)** patient satisfaction with care; and **C)** provider TBP construct scores at control and intervention sites.

2) Comparative analyses – To identify patient-, provider-, and/or clinic-level factors independently associated with adoption and maintenance of intervention components, we will develop linear or logistic regression models, taking into account the clustered design (for example, robust standard errors). To compare by study arm the change from baseline (pre-randomization) to post-intervention in **A)** patient cost; **B)** patient satisfaction with care; and **C)** TPB construct scores, we will use a cluster-level analysis, similar to methods described for the primary outcome under Aim 1. The analysis will take into account the stratified design and an adjusted analysis will also be conducted taking into account other baseline imbalances by study arm.

3) Qualitative analyses – De-identified focus group or interview transcripts will be uploaded to the qualitative data analysis software Dedoose (SocioCultural Research Consultants, USA). Thematic interpretation[87-89] will include collaborative development of a coding framework and detailed coding of transcripts using Dedoose. Coded transcripts will be sorted to identify thematic groupings. The thematic groupings will be reviewed to identify emergent themes within each domain of the coding framework and quotes that best represent each domain. Thematic interpretation will focus on individual, social and structural factors associated with successful or unsuccessful adoption and/or maintenance of the intervention components at different sites

The sample size for Aim 2 analyses is either fixed (process metrics; provider surveys and focus groups) by parameters of the clinical trial or based on feasibility considerations (patient surveys and provider in depth interviews). For quantitative analyses, the sample size is sufficiently large (data on 3400 patients for process metrics analyses, 800 patient surveys, and 100-200 provider surveys) to enable multivariable analysis to identify factors associated with intervention adoption and maintenance.

Potential problems and alternative strategies. We do not anticipate problems with quantitative or qualitative data collection – we have ample experience doing similar work as proposed here at health centers in Uganda (see Section 3.3.2). Furthermore, we believe the goals of Aim 2 are important, whether or not the SIMPLE TB strategy proves effective in achieving the outcomes laid out in Aim 1. The information gained will be critical for revising the conceptual model and/or re-thinking the choice of intervention components to be tested in future studies, and to theory development in implementation science.

Aim 3. To compare the costs and epidemiological impact of standard and SIMPLE TB diagnostic evaluation strategies.

Introduction. The overall objective of this aim is to estimate the incremental cost-effectiveness and the population-level epidemiological impact (10-year reductions in TB incidence and mortality) of the SIMPLE TB strategy in Uganda. Our working hypothesis is that the SIMPLE TB strategy will be both effective and cost-effective (*i.e.,* that the SIMPLE TB strategy will improve effectiveness at an incremental cost that would fall below international standards of highly cost-effective interventions).[90] Our rationale is that evidence-based estimates of cost and impact are essential for appropriate policy making in TB control, and we intend for this research to influence the emerging TB elimination strategy in Uganda and elsewhere. Our findings will have long-term impact by providing some of the first practice-informed estimates of the cost-effectiveness and population-level impact of scaling up a patient-centered TB diagnostic evaluation strategy in a high-burden country, thus facilitating decisions on whether such a strategy should be prioritized for TB elimination.

Procedures and Measurements. We will conduct an empirical costing study across all 22 sites, including collection of cost data from both health system and patient perspectives. From the health system perspective, we will use a combination of detailed budgetary analysis, interviews of key staff members, logbooks and/or timesheets to record proportions of staff time devoted to various activities, and direct observation (e.g., time-motion studies of at least 10 patients and 3 staff members per clinic) to estimate the incremental cost of the SIMPLE TB strategy relative to current standard practice. From the patient perspective, we will utilize data on direct and indirect costs associated with TB diagnostic evaluation collected as part of Aim 2. We will use, in our primary analysis, an "ingredients" or bottom-up approach[68], comparing this to a top-down approach (for the health system perspective) based on centralized budgets and interviews. Our costing exercise will be comprehensive, including costs associated with each component of the SIMPLE TB strategy and outcomes (*e.g.,* TB treatment) necessary to estimate incremental effectiveness.

Data Analysis.

Cost-effectiveness – Our primary outcome will be the incremental cost-effectiveness of the SIMPLE TB strategy from a societal perspective, measured as the cost per disability-adjusted life year (DALY) averted relative to standard TB evaluation. Secondary outcomes will include 1) the incremental cost of introducing and maintaining the SIMPLE TB strategy (a measure of affordability for health systems) and 2) the incremental patient cost per diagnostic evaluation and per treatment initiated (a measure of affordability and access for patients). For all outcomes, we will report stratified results for key populations including women and people living with HIV. To assess cost-effectiveness, we will use the primary effectiveness data from Aim 1 and relevant literature estimates (*e.g.,* clinical outcomes among those initiating treatment) to construct a Markov model including states for undiagnosed TB but seeking care, undiagnosed TB not seeking care (e.g., because initial diagnostic evaluation was too expensive), treated TB, self-resolved TB, and death. States will be subdivided according to smear and Xpert status (smear-positive, smear-negative/Xpert-positive, and smear/Xpert-negative) and HIV status (positive and negative, on/off ART, with CD4 strata). Data to inform transition probabilities and health utilities will come from study data where feasible (including specific questions of patients to ascertain probabilities such as future care-seeking if diagnoses are missed), and the literature where unavailable. We will follow international conventions for all procedures including economic costing, discounting, and reporting.[91] We will conduct one-way sensitivity analyses across all model parameters, multi-way sensitivity analyses for those parameters found to be most influential, and a probabilistic uncertainty analysis in which all parameters are varied simultaneously using Latin Hypercube Sampling.

Population-Level Epidemiological Impact – We will construct a compartmental epidemic model of TB in Uganda to evaluate the potential impact of scaling up the SIMPLE TB strategy across a representative district in Uganda. Using our team's prior models of TB diagnostics in India[71] and sub-Saharan Africa[70] as a starting point, we will construct a population model that includes structure both for TB natural history (e.g., latent, subclinical, pre-diagnostic, diagnosis-seeking, treated)[92] and steps in the diagnostic cascade (e.g., pursuing diagnosis, diagnosed but not treated, treated).[71, 72] We will include structure for both HIV and MDR TB, and will link this model's structure to that of the Markov model constructed for cost-effectiveness analysis above (for purposes of explicitly estimating the importance of transmission to considerations of cost-effectiveness). We will fit the model to epidemiological data from a selected representative district in Uganda according to its TB incidence, prevalence, and mortality, as well as additional factors including prevalence of HIV and of MDR-TB. This model will project TB incidence and mortality over a primary time-frame of 10 years under two alternative scenarios: 1)

standard TB diagnostic evaluation and 2) streamlined TB diagnostic evaluation using the SIMPLE TB strategy. In a secondary analysis, we will incorporate economic data as described above, comparing cost-effectiveness measured under a dynamic (epidemic-economic) framework to that of the Markov model. The dynamic transmission model has the advantage of incorporating transmission dynamics at the population level, but requires more assumptions (*e.g.*, homogeneous mixing in the source population). By comparing results from Markov and transmission modeling, we will be able to assess: 1) the relative contribution of population-level transmission to the overall effectiveness and cost-effectiveness of different TB diagnostic evaluation strategies over time and 2) the relative influence of given model parameters on cost- effectiveness under a cohort-based versus transmission-based evaluation model.

Potential problems and alternative strategies. Several challenges could arise in the proposed Aim 3 analyses. First, if the SIMPLE TB strategy is both more costly and less effective than standard TB evaluation, it will clearly not be preferred to standard TB evaluation. However, in this (unlikely) case, we can use our modeling approach to explore the key drivers of cost-effectiveness and impact for other strategies that seek to streamline the TB diagnostic system in high-burden areas, and also to describe settings in which SIMPLE TB or other such interventions are more likely to achieve important population-level impact of cost-effectiveness. Second, challenges could arise in collecting cost and utility data, such as high between-site variance in cost estimates and effectiveness outcomes. In this case, we will perform sensitivity analyses across the range of cost and utility data to determine the impact of the variance on overall outcomes.

3.3.4 Timeline

Specific Aims	Year 1	Year 2	Year 3	Year 4	Year 5
Aim 1: Yield, efficiency, impact of TB diagnostic evaluation strategies					
a) Site selection, baseline data collection and randomization	●				
b) RCT of standard vs. SIMPLE TB diagnostic evaluation strategies		●	●	●	
c) Data analysis and presentation of results				●	●
Aim 2: Adoption, implementation and maintenance of SIMPLE TB strategy					
a) Quantitative analysis of process metrics and patient/provider surveys	●	●	●	●	●
b) Qualitative data collection from health workers				●	●
c) Data analysis and presentation of results				●	●
Aim 3: Cost-effectiveness and population impact modeling					
a) Cost-effectiveness analyses and presentation of results	●	●	●	●	●
b) TB incidence/mortality impact modeling and presentation of results				●	●

3.3.5 Future Directions: When the proposed analyses are complete, we will have produced a comprehensive description of whether the SIMPLE TB strategy can overcome barriers to high-quality TB diagnostic evaluation and improve linkages to care. Furthermore, we will have estimated the cost-effectiveness and epidemiological impact of the SIMPLE TB strategy. Depending on our results, we will be prepared to move in one of two possible future directions. If the SIMPLE TB strategy is effective and scalable, we will seek to utilize its infrastructure (sputum transport, SMS-based results reporting) to support active case finding in the community (*i.e.*, TB screening in high risk settings or communities), which is important to further reduce transmission.[93] If, however, the SIMPLE TB strategy is not effective, we will refine the intervention (*e.g.,* patient or health worker incentives) or the implementation process (*e.g.,* enhanced training and feedback) based on our findings. In either case, our focus will be on generating practice-based evidence on how to best deliver high-quality, patient-centered TB diagnostic evaluation services in high burden countries.

4. HUMAN SUBJECTS RESEARCH

The proposed research activities qualify as Human Subjects Research and meet the definition of “Clinical Research,” as described fully below.

4.1. RISKS TO THE SUBJECTS

Human Subjects Involvement and Characteristics: In order to reach the WHO’s goal of reducing incidence and prevalence of TB, and of ultimately eliminating TB, better strategies will be required to ensure that patients with TB who present for care are identified and treated. Currently, a large proportion of patients who present for care to community health centers are lost to follow-up before TB can be diagnosed and treated. Principle reasons include inconvenience to patients of the standard approach to TB diagnostic evaluation, lack of systems to link patients to novel diagnostics such as Xpert MTB/RIF (**Xpert**) available at higher-level facilities, and lack of

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