Clinic versus Hotspot Active Case Finding and Linkage to Preventive Therapy (ACF/TPT) Strategy Evaluation for TB: A Cluster-Randomized Crossover Trial *(CHASE-TB)*

National Clinical Trial (NCT) Identified Number: NCT05285202

Principal Investigators: Emily Kendall, MD PhD, and David Dowdy, MD PhD

Grant Title: Hotspot versus clinic-based active case finding for TB in Uganda: A pragmatic randomized trial

Grant Number: 2R01HL138728

Funded by: National Heart, Lung, and Blood Institute

Version Number: v2.3

18 May 2026

CONFIDENTIALITY STATEMENT

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Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

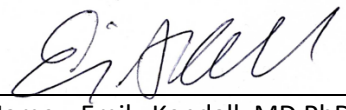
National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol (formatted according to Institutional Review Board [IRB] guidance), informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator:

Signed:  Date: 18 May 2026

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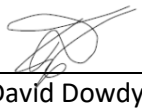
Signed:  Date: 18 May 2026

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Clinic versus Hotspot Active Case Finding and Linkage to Preventive Therapy (ACF/TPT) Strategy Evaluation for TB: A Cluster-Randomized Trial *(CHASE-TB)*

Grant Number: 2R01HL138728

Study Description: This five-year study will evaluate two strategies for conducting tuberculosis (TB) active case finding (ACF) and linkage to TB treatment or TB preventive therapy (TPT) in peri-urban Uganda. The two strategies differ in the location where ACF activities are performed: A "facility-based" ACF/TPT strategy will perform ACF, plus linkage to TPT, in the immediate vicinity of a large public health facility and will primarily recruit individuals who are attending the health facility, irrespective of TB suspicion or symptoms. Alternatively, a "hotspot-based" strategy will use routine notification data and local expertise to identify local TB hotspots – defined as the geographic areas though to have the highest burden of undiagnosed TB per estimated population. The same infrastructure (personnel, equipment, supplies, etc.) for ACF/TPT will then be placed in those parishes for a period of four months at a time, and the general population will be recruited for screening and linkage to TPT.

The two interventions will be compared in a Type 1 hybrid effectiveness-implementation trial with a cluster-randomized, multiple-period crossover design. We hypothesize that hotspot-focused ACF/TPT will result in a greater number of TB patients diagnosed and linked to care, and a greater number of individuals started on preventive therapy, than facility-based ACF/TPT. Secondarily, we will also compare the two interventions in terms of number of people initiated on TPT, and we will compare TB cases detected in regions performing ACF/TPT (either approach) against cases detected in regions that continue to perform the standard of care.

Objectives:

Primary Objective:

- Compare two TB active TB case-finding interventions in terms of effectiveness at increasing TB diagnosis and treatment

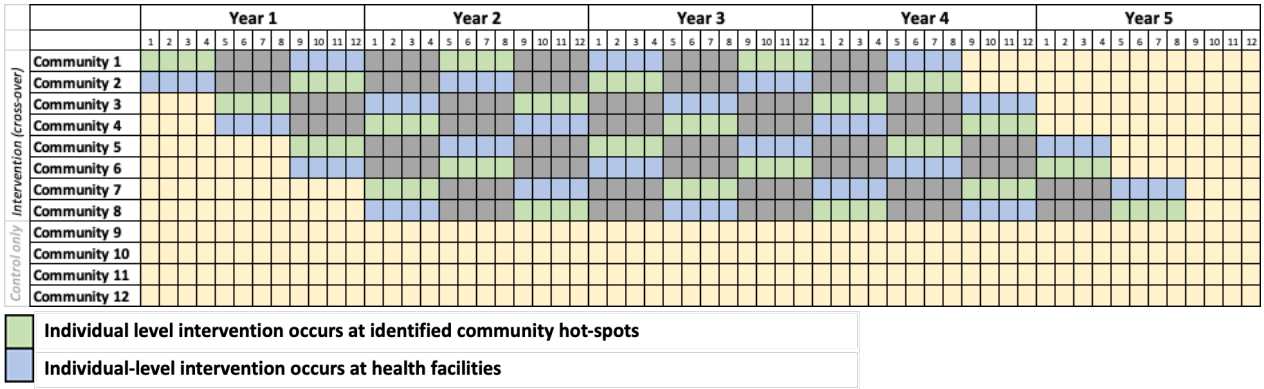
Secondary Objectives:

- Compare two TB active TB case-finding interventions in terms of effectiveness in increasing uptake of TPT
- Estimate impact of active TB case-finding interventions on TB treatment initiations and population TB burden, compared to no intervention
- Compare the implementation of the two interventions
- Estimate costs and cost effectiveness of any ACF/TPT intervention that is effective

Endpoints:	• *Number of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing periods in which regions performed hotspot-focused ACF/TPT to those in which facility-based ACF/TPT was performed (Primary endpoint).* • *Number of study region residents initiating TPT during intervention periods* • *Number of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing intervention regions to control regions* • *Trend in TB notification rate over the span of study intervention involvement, comparing intervention clusters to control clusters* • *Number of people diagnosed with TB through study participation and initiating treatment for TB, comparing hotspot-focused to facility-based ACF/TPT* • *Total number of people screened for TB with each intervention (as part of characterizing screening cascades)* • *Number of study participants found to have Xpert-positive sputum (as part of characterizing screening cascades)* • *Incremental cost per disability-adjusted life year (DALY) averted, comparing the more to the less effective ACF/TPT intervention (if an effectiveness difference is found).* • *Incremental cost per disability-adjusted life year (DALY) averted, comparing ACF/TPT to no ACF/TPT.*
Study Population:	*Age >=15 years, and TB contacts >= 5 years, in Uganda*
Description of Sites/Facilities Enrolling Participants:	*12 large peri-urban health facilities and their surrounding catchment areas in Central and Eastern Uganda*
Description of Study Intervention/Experimental Manipulation:	*Screening for TB using mobile chest X-ray with computer-aided interpretation, and confirmatory sputum Xpert MTB/RIF Ultra testing for those with X-ray abnormalities above a specific threshold, with referral to TB treatment services if positive. For those not diagnosed with active TB, assessment for TPT eligibility (including tuberculin skin test if indicated) and linkage to TPT if eligible.* *At a cluster level, implementation of this package of active TB case finding and linkage to TPT either on the grounds of health facilities or in communities thought to have a high burden of undiagnosed TB.*
Study Duration:	*60 months*
Participant Duration:	*10 to 60 minutes of interaction with study staff; up to 1 week to receive results if confirmatory sputum testing is required*

1.2 SCHEMA

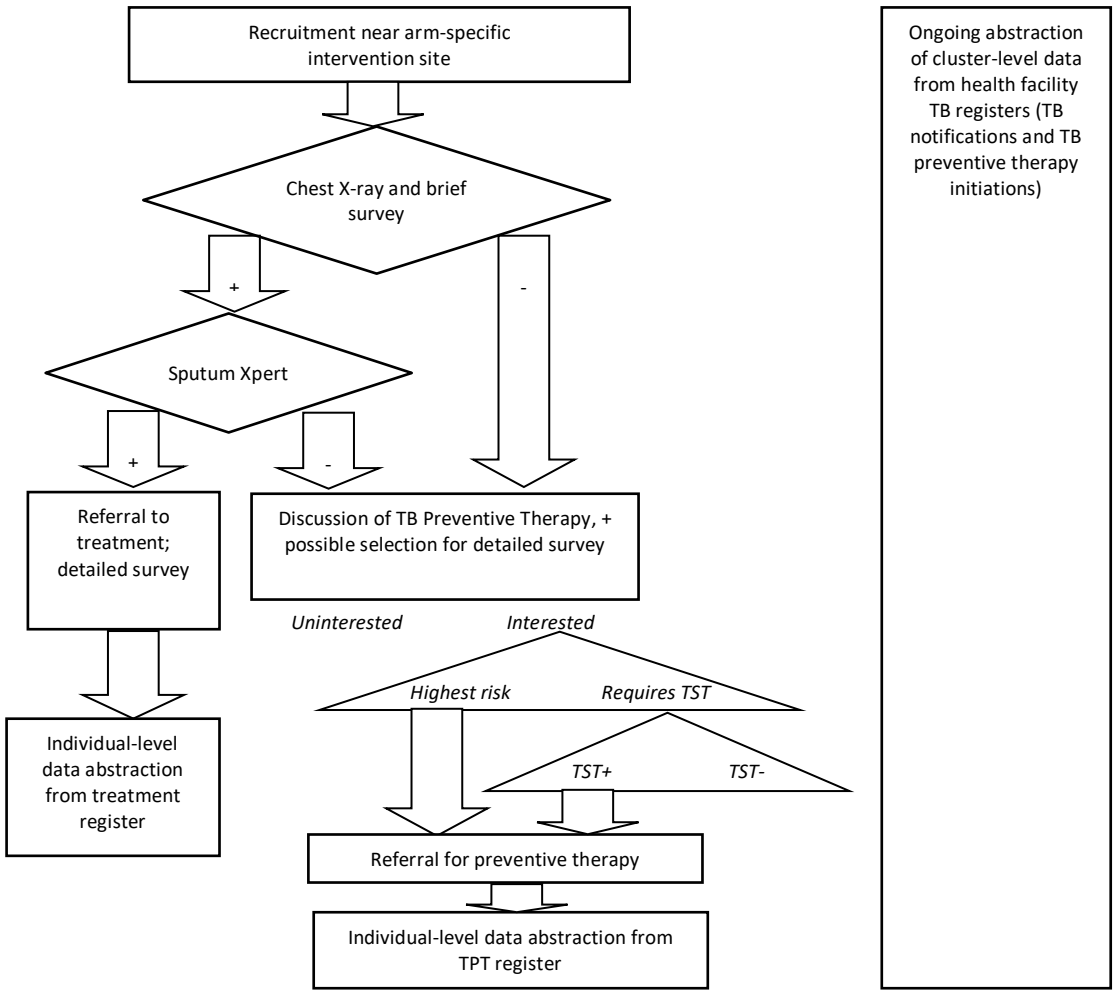
1.2.1 CLUSTER-LEVEL STUDY DESIGN AND TIMELINE



The originally planned study timeline is illustrated above. Based on accrual, budget, and funding timeline considerations, a decision was made in February 2026 to end the study after the 12 intervention periods shown in Years 1-4, and to forego the final intervention period in Communities 5-8.

1.2.2 INDIVIDUAL-LEVEL INTERVENTIONS:

Individual participants will receive the same interventions for active case-finding and linkage to preventive therapy in both arms:



1.3 SCHEDULE OF ACTIVITIES

	First study contact (within 4-month intervention periods)	Follow up after sputum collection (within 2 weeks of testing if possible)	Follow up after TST placement (40-96 hours)	Register review (conducted at least quarterly, with more frequent targeted confirmation of linkage to care)
Recruitment	X			
Oral Consent	X			
Demographics	X			
TB symptoms	X			
Clinical history	X			
Digital chest X-ray	X			
Sputum TB testing (Xpert MTB/RIF)	if chest X-ray abnormal			
Contact patient by phone once sputum result available		X		
Attempt to visit patient if unable to reach by phone		If sputum positive		
Detailed interview	If randomly selected after x-ray	If sputum positive and not already interviewed		
Referral for TB treatment		If sputum positive		
TPT counseling	If high-risk and potentially eligible (excludes those with abnormal x-ray and symptoms who will require further evaluation for active TB even if Xpert negative)			
TST placement if interested in TPT	If HIV-/unknown and potentially TPT eligible			
TST reading			X	
Referral for TB preventive therapy	If HIV+ or contact declining TST, and X-ray negative	If HIV+ or contact declining TST, and sputum negative	If TST+	
Referral for further clinical evaluation		If symptomatic or a known contact, with concerning x-ray but sputum Xpert negative/unavailable		

	First study contact (within 4-month intervention periods)	Follow up after sputum collection (within 2 weeks of testing if possible)	Follow up after TST placement (40-96 hours)	Register review (conducted at least quarterly, with more frequent targeted confirmation of linkage to care)
Assessment of linkage to care and outcomes				If referred for treatment, preventive therapy, or further clinical evaluation

2 INTRODUCTION

2.1 STUDY RATIONALE

Tuberculosis (TB) is one of the 10 leading causes of death worldwide, responsible for 1.2 million deaths every year.[1] Of the 10 million people who develop TB disease each year, nearly 3 million are never diagnosed and reported.[1] While some of this gap reflects treatment in the private sector and/or inadequate reporting, a sizeable component represents undiagnosed TB. National TB prevalence surveys in Africa and Asia have consistently found that, for every person diagnosed and reported with TB in a given year, at least one – and often as many as three – people have undiagnosed prevalent TB in the community.[2,3] Approximately half of these undiagnosed prevalent cases are sputum smear-positive, suggesting that undiagnosed TB serves as a major source of ongoing transmission. It is therefore unlikely that substantive reductions in TB transmission can be made without finding people with undiagnosed TB earlier in their disease course.

In addition to the <1% who have undiagnosed "active" TB disease at any moment, an estimated 23% of the world's population is infected with *M. tuberculosis*, with ongoing potential to progress to TB disease.[4] It is increasingly clear that treatment of latent TB infection (LTBI) – also known as TB preventive therapy (TPT) – is an essential component of any intervention aiming to substantially reduce population-level TB burden.[5–7] Since a necessary step in providing TPT is to first rule out active TB, ACF offers a unique opportunity to expand TPT by screening a broader population for TB disease (and thus TPT eligibility). However, to date, ACF campaigns have largely focused on diagnosing and treating TB disease rather than LTBI, primarily due to concerns of cost and feasibility. A feasible approach to implementing both ACF and TPT in the community could therefore have transformative impact.

Key technological innovations have converged to make community-based campaigns to provide ACF and TPT increasingly feasible over the past five years. First, whereas TPT has historically involved six months or more of daily isoniazid, novel regimens have shortened the duration of treatment to twelve weeks (of either weekly rifapentine plus isoniazid or daily rifampin plus isoniazid) while simultaneously reducing the frequency of adverse drug reactions.[8–10] By reducing the burden on the healthcare system for drug delivery and monitoring – and thus costs as well[11] – these new regimens may make community-based provision of TPT increasingly feasible in the coming 3-5 years.

In addition to novel TPT regimens, innovations in X-ray technology are expanding access to population-level screening for TB disease. New mobile chest X-ray units, for example, enabled the screening of over 34,000 people in Vietnam in under four months.[12] Similar mobile X-ray screening programs have been recently

implemented in India,[13] the Philippines,[14] rural Cambodia,[15] Zimbabwe,[16] and elsewhere. Furthermore, novel artificial intelligence (AI)-based software systems for reading chest X-rays now equal or surpass the accuracy of radiologists in identifying people with and without TB disease.[17,18] As a result, chest X-rays for TB screening can now be read in automated fashion within minutes, making mass screening of large populations a realistic possibility; indeed, chest X-ray screening with computer aided detection was endorsed by the World Health Organization (WHO) in 2020.[19] However, despite growing utilization worldwide, very little comparative evidence exists to inform the optimal approach to X-ray screening, in terms of both effectiveness and implementation.

Third, innovations in confirmatory sputum-based TB testing have made highly sensitive point-of-treatment TB diagnosis feasible in community settings. The new Xpert Ultra cartridge (Cepheid, Inc, Sunnyvale, CA) has a sensitivity for TB disease that approaches that of a single TB culture,[20] but can deliver results in two hours rather than many weeks. During the initial R01 award period, our team performed Xpert Ultra testing on over 12,000 individuals in Kampala, Uganda[21], demonstrating the feasibility of Xpert testing in our proposed study area. We are therefore now well positioned to leverage our initial findings into a trial of community-based TB screening and prevention. In summary, a combination intervention consisting of mobile chest X-ray, AI-based X-ray reading, confirmatory testing with a rapid high-sensitivity diagnostic (Xpert Ultra), and provision of TPT (including new short-course TPT regimens) to those without active TB is now, for the first time, feasible to implement at the community level in high-burden countries. While each component of this intervention has been rigorously tested, it remains unclear how best to implement all components in combination.

Our trial will therefore evaluate the comparative effectiveness and implementation of this combination intervention under two different approaches: a clinic-based strategy that incorporates existing infrastructure and patient preferences, and a "hotspot-focused" approach that brings testing and treatment directly to neighborhoods experiencing the highest burden of TB.

Specifically, we will conduct a multiple period, cluster randomized crossover trial[22] to evaluate facility-based versus "hotspot"-based ACF, with linkage to TPT, in eight intervention regions surrounding Kampala, Uganda (with four additional regions randomized to no interventions). This trial is conceptualized as a type 1 hybrid effectiveness-implementation design. In the first ("facility-based") strategy, we will conduct TB screening and linkage to TPT from tents adjacent to the major health facility. This strategy leverages existing healthcare infrastructure and the stated preference of participants in an earlier case-finding study to be screened while visiting their local health facility. In the alternative ("hotspot-focused") strategy, we will use routine notifications and other available data to identify geographic areas likely to have a high burden of undiagnosed TB, and we will deploy similar mobile TB screening centers to venues (e.g., markets, public buildings, taxi stands) in these "hotspot" regions. Both strategies will leverage novel technologies, including mobile chest X-ray with artificial intelligence (AI)-based reading, the highly sensitive Xpert Ultra test for confirmation, and a patient-centered approach of LTBI testing plus linkage to TPT for participants who are interested. Both strategies will also be compared against control regions implementing the standard of care. The primary clinical effectiveness outcome of interest will be the number of individuals starting treatment for bacteriologically confirmed new or relapsed pulmonary TB, with a secondary outcome of the number of individuals initiating TPT.

2.2 BACKGROUND

Intensive efforts to find individuals with undiagnosed TB (i.e., active case finding, ACF) can achieve profound reductions in TB burden.[23] For example, three years of annual population-based screening resulted in a 44%

reduction in prevalence across 60 communities in southern Vietnam.[24] A remarkably similar 41% reduction in prevalence was seen following six rounds of twice-yearly screening using a mobile van in Harare, Zimbabwe.[25] Unfortunately, interventions with lower levels of population coverage have not been as successful – for example, in 24 communities of Zambia and South Africa, interventions that obtained sputum from 5-12% of the underlying population (versus, for example, 35-45% *per year* in Vietnam) did not result in statistically significant reductions in TB prevalence.[26] A critical question, therefore, is whether ACF can be implemented in a manner that is sufficiently intensive to be epidemiologically impactful, yet sufficiently focused to be economically and logistically infeasible. Our proposed trial will fill this important knowledge gap by testing the two most promising strategies identified during an initial community survey in Kampala, Uganda.

In addition, modeling studies suggest that coupling ACF and TPT could generate synergistic population-level impact on TB incidence and mortality.[27] One of the few community-based efforts to provide ACF and TPT (in Bethel, Alaska) witnessed a decline in the annual risk of TB infection from 24% in 1949-1951 to 8% in 1957 to 1% in 1960.[28] Thus, strong empirical and theoretical evidence suggests that a combined approach to ACF and TPT can have major impact on TB burden at the community level.

Uganda has a high burden of TB, with an estimated adult prevalence in 2014-2015 of 401 per 100,000 people (95% confidence interval: 292-509).[29] Uganda's national TB prevalence survey indicated that there were three prevalent TB cases for every annual notification, that over 40% of undiagnosed prevalent TB was smear-positive (indicating high transmission risk), and that 90% of all people with undiagnosed prevalent TB had abnormalities on chest X-ray.[29] Uganda is also representative of low-income countries, with a per-capita gross domestic product (GDP) of $794, placing it among the poorest 20 countries in the world.[30] Despite its relative lack of financial resources, Uganda has a robust TB research infrastructure and is committed to scale-up of ACF and TPT. For example, Uganda's National Tuberculosis and Leprosy Programme (NTLP) recently purchased a mobile chest X-ray unit and is also supporting multiple trials of short-course preventive therapy.

Our specific study interventions are motivated by findings of a recent study conducted in Kampala, STOMP-TB. This study tested >12,000 adult residents of a defined community for TB using the sputum Xpert Ultra test. It found that the five zones in the study area with the highest baseline notification rates (per 100,000 population) accounted for only 22% of the community's population but 62% of all notifications – and also 46% (95% confidence interval: 35 – 56%) of all undiagnosed prevalent cases– both of which, according to simulation analysis, were significantly higher than would be expected by statistical chance ($p<0.001$).[31] These findings suggest that hotspot-focused strategies could be more efficient than geographically untargeted approaches, and that routine notifications can identify hotspots without the need for more advanced analysis that is typically unavailable in high-burden settings. The STOMP study also identified venue-based screening as an intervention that recruited a different and higher-risk population than door-to-door screening. And finally, STOMP-TB participants identified health facility waiting areas as their most preferred TB screening location. This stated preference, together with the logistical benefits of facility-based testing for facilitating linkage to care after a positive result, suggests facility-based screening as a promising alternative to hotspot-based TB screening.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Our study is designed to use interventions that could be widely implemented with minimal risk to participants.

The primary risk is a breach of confidentiality. Participants will be asked to provide potentially sensitive information (e.g., TB and HIV status). While every effort will be made to maintain those data in confidential and secure fashion, it is possible that data could become known by individuals other than study personnel.

Minor clinical risks include:

- Chest X-ray (for all non-pregnant participants): In theory, radiation exposure carries risk of DNA damage and carcinogenic effects. The radiation dose associated with a single chest X-ray is less than the typical weekly exposure to background radiation exposure on the earth's surface.
- Tuberculin skin test (TST, for high-risk participants who wish to consider preventive therapy if TB-negative and TST-positive): TST is used in routine clinical practice and occupational screening to assess for TB exposure. Its risks include brief discomfort from subcutaneous injection; injection site allergic reactions; transient maculopapular rash (1 per 2000 to 3000); and systemic allergic reaction (1 per 1-3 million, similar to the rate of anaphylaxis with routine vaccines). Blood testing for TB infection (using interferon gamma release assays) was considered as an alternative, but was not pursued because of the logistical complexity of collecting blood and performing this test in community settings, and because of these tests' prohibitive costs for programmatic implementation in the study setting.

Finally, participants will experience a small cost of time/inconvenience from participating, and those who return for an Xpert or TST result may incur transportation costs.

2.3.2 KNOWN POTENTIAL BENEFITS

For participants who are diagnosed with TB through our study, the ability to promptly start curative treatment promptly is likely to have the clinical benefits of preventing future symptoms/morbidity associated with progressive disease, and potentially preventing permanent lung damage or mortality from delayed TB treatment. Similarly, individuals diagnosed with latent TB infection will be offered treatment that prevents progression to active TB disease, thereby preventing additional morbidity and mortality as well.

At a population level, intensive diagnosis and treatment of TB is likely to result in reduced transmission within our study sites, thereby lowering the incidence of one of the leading causes of death (i.e., TB) in study communities. The knowledge gained from this study will also be of benefit to the larger scientific and policy communities (particularly in Uganda), as it will guide policymakers in optimally allocating scarce resources for TB control and prevention.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We will take every effort to protect against a breach of confidentiality. Study data will be maintained on a secure research database (REDCap), with access restricted to study personnel. Data collectors and managers will be asked to sign a confidentiality agreement prohibiting disclosure of any patient-level information. All communications involving study data will be encrypted. Datasets for analysis will be de-identified prior to sharing, and when possible (e.g. for participants who do not need to be tracked in treatment registers), identifying data will be deleted after results have been returned.

Chest X-ray screening and tuberculin skin testing are used routinely in clinical practice and are recommended by WHO and others for screening patients of comparable risk level to our study population. Their risks are judged to be minimal and to be outweighed by the health benefits of TB prevention or early detection, but the risks will also be mitigated as follows:

Only one X-ray view per participant will be used to characterize the probability of TB, and women known to be pregnant will be allowed to bypass the screening step and go directly to sputum testing. Women wishing to take a pregnancy test before undergoing chest X-ray will be offered a pregnancy test free of charge.

We will only test participants with TST after we have verified that that they would be eligible for TPT with a positive TST (and with a negative Xpert result, for x-ray positive individuals whose sputum test is pending), that they are not TPT-eligible regardless of TST result, and that they are willing to take TPT if eligible. All participants will be able to decline TST without adversely affecting their participation in the study – indeed, the proportion of participants who accept vs. decline TST after learning of the risks and benefits is of interest to our research aims. In April 2024, we further limited TST to participants who were high risk based on recent close contact with someone who had TB, due to lower than expected completion and positivity rates of TST in the general population.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Compare two active TB case-finding interventions in terms of effectiveness at increasing TB diagnosis and treatment	Number of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing periods in which regions performed hotspot-focused ACF/TPT to those in which facility-based ACF/TPT was performed.	This outcome captures the actual difference in number of people with TB who are treated, in that it includes diagnoses that would not have been made without the intervention as well as diagnoses that were made more quickly because of the intervention – but it does not give “credit” for diagnoses simply made in a different location to another (e.g. in the ACF/TPT tent rather than the clinic). The endpoint is conservative in

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		excluding participants from outside the study region and participants who may seek care at nonparticipating health facilities or after the intervention period. Since we cannot enroll each study region's entire population, we use a count (rather than rate or proportion) of TB notifications. We chose this measure as being most relevant from a public health perspective, for an intervention that seeks to optimize the number (rather than proportion) of people diagnosed and treated for a given resource outlay.
Secondary		
Compare two active TB case-finding interventions in terms of effectiveness in increasing uptake of TPT	Number of study region residents initiating TPT during intervention periods, comparing periods in which regions performed hotspot-focused ACF/TPT to those in which facility-based ACF/TPT was performed	TPT initiation is a secondary objective of the ACF intervention, which can enhance the impact of ACF and can be facilitated when ACF excludes active TB. Analysis will be stratified before/after April 24, 2024, when we limited TPT referral eligibility to contacts and people with HIV.
Estimate impact of active TB case-finding interventions on TB treatment initiations and population TB burden, compared to no intervention	Number of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing intervention regions to control regions Average percent change in number of TB notifications, from the first 16 months of intervention to the final 16 months of intervention, comparing intervention clusters to control clusters Number of people diagnosed with TB through study participation and initiating treatment for TB, hotspot-	Even if no difference is found between the two versions of the intervention, it is important to estimate whether either or both increases TB treatment initiations relative to no intervention, and whether the result of increased ACF and/or TPT is to reduce over time the number of prevalent TB cases requiring notification and treatment.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	focused and facility-based ACF/TPT	
Compare the implementation of the two interventions	Total number of people screened for TB with each intervention Number of study participants found to have Xpert-positive sputum Number of people screened for TB who are identified as contacts of a person diagnosed with TB through the study	Descriptive analysis and comparison between arms may identify strengths and limitations of each intervention
Estimate costs and cost effectiveness of any ACF/TPT intervention that is effective	Incremental cost per disability-adjusted life year (DALY) averted, comparing the more to the less effective ACF/TPT intervention (if an effectiveness difference is found) Incremental cost per disability-adjusted life year (DALY) averted, comparing ACF/TPT to no ACF/TPT	Costs and cost-effectiveness are likely to be critical to any scale-up or implementation decisions at the policy level.
Tertiary/Exploratory		
Compare intervention effectiveness to a control of national trends	Average percent change in number of TB notifications, from the first 16 months of intervention to the final 16 months of intervention, comparing intervention clusters to the national notification rate	If our intervention reduces TB incidence over time, then TB notifications may decline more quickly in intervention clusters (including intervention periods in both the initial and the final measurements) than in Uganda as a whole
Compare the implementation of the two interventions	Proportion of participants found to have active TB Change in the above outcomes over time, within intervention periods, or across intervention periods in the same region	Descriptive analysis and comparison between arms may identify strengths and limitations of each intervention

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Understand how reach and effectiveness differ by sex, location, and clinical covariates	Key effectiveness and implementation outcomes (including TB notifications, reach of screening, and TB prevalence among those screened) stratified by age, sex, HIV status, subcounty/parish of residence, TB symptom prevalence and duration, contact status, and health care access indicators (see Subgroup Analyses below)	It is important to understand how reach and effectiveness differ across readily identifiable demographic subgroups.
Describe cascades of care associated with each intervention	Number of people completing each screening step, as a proportion of those eligible for that step Number of contacts completing each screening step Number of contacts diagnosed with TB Self-reported barriers to TST reading, among those completing and not completing Clinical TB diagnosis and TB-unrelated medical diagnoses and treatments resulting from xray screening	Understand hurdles to achieving maximal impact with each intervention, so that they may potentially be addressed
Estimate costs and cost effectiveness of any ACF/TPT intervention that is effective	Empiric costs of study interventions from a health systems perspective Incremental cost per incremental person initiating treatment for bacteriologically confirmed new or relapsed TB Incremental cost per incremental person initiating TPT	Costs and cost-effectiveness are likely to be critical to any scale-up or implementation decisions at the policy level.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Estimate impact of ACF/TPT interventions on diagnostic delays	Reduction in time to TB diagnosis when notification time trends are fit to a simulation model of TB care seeking	A key motivation for active case finding is to reduce the amount of time to diagnosis and initiation of treatment.
Estimate impact of ACF/TPT interventions on population-level TB burden	Change in 10-year TB incidence and mortality in a transmission model of intervention scale-up	We hope that this intervention may have epidemiological impact at the population level in reducing TB burden.
Estimate potential impact of an intervention to treat X-ray-positive, Xpert-negative subclinical TB during ACF	One-year incidence of notified TB among participants with abnormal X-ray and negative sputum	The impact of X-ray based TB screening could be increased by treating early, radiographically evident disease.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This five-year, multiple-period crossover, cluster-randomized, Type I implementation-effectiveness trial will evaluate two strategies for conducting tuberculosis active case finding (ACF) and linkage to TB treatment or TB preventive therapy (TPT) in peri-urban Uganda. The two strategies differ in the location where ACF activities are performed: A “facility-based” ACF/TPT strategy will perform ACF, plus linkage to TPT, in the immediate vicinity of a large health facility and will primarily recruit individuals who are attending the health facility, irrespective of TB suspicion or symptoms. Alternatively, a “hotspot-based” strategy will use routine notification data and other characteristics to identify local TB hotspots – defined as the geographic parishes deemed likely to have the highest burden of undiagnosed TB. The same infrastructure (personnel, equipment, supplies, etc.) for ACF/TPT will then be placed in those parishes for a period of four months at a time, and the general population will be recruited for screening and linkage to TPT.

We hypothesize that periods of hotspot-focused ACF/TPT will result in a greater number of TB patients diagnosed and linked to care, and a greater number of individuals started on preventive therapy, than periods of facility-based ACF/TPT. Secondarily, we will also test the hypothesis that regions implementing the two ACF/TPT interventions will have more TB cases detected and more people initiated on TPT, than regions that continue to perform the standard of care.

The two interventions will be compared in a Type 1 hybrid effectiveness-implementation trial with a cluster-randomized, multiple-period crossover design. The clusters will consist of twelve non-overlapping, peri-urban geographic “study regions” (eight of which will receive the study interventions) surrounding Uganda’s capital of Kampala. Each contains a central healthcare facility (level III health center or higher; most are district hospitals) from which most TB cases in the region are notified, and each has capacity for both molecular TB diagnosis and

provision of TB preventive therapy. The twelve study regions (clusters) will be grouped by the study statistician into groups of three ("triplets") in a way that minimizes the differences in certain key baseline characteristics, and within each triplet, two regions will be randomized to alternating sequences of interventions (ABABAB or BABABA), while the third will be randomized to the standard of care (with periodic reviews of TB diagnosis and treatment registers). Study PIs will be blinded with respect to which outcome data come from which facility, but no other allocation concealment will be possible.

Each intervention period will last four months, followed by a four-month washout period before starting the other intervention. Start times will be staggered, with two clusters starting their first intervention in each of the first four periods. As originally designed, each of the eight regions assigned to interventions would receive a total of 12 months of each intervention (3 four-month periods of each intervention type) over four years, as illustrated in section 1.2. Due to a decision to terminate the study 8 months early, four of the regions will ultimately receive only 5 four-month intervention periods (3 of one type, 2 of the other). The final four regions will serve as controls for secondary analyses.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This multiple-period, cluster randomized design will: (a) enable fair comparison between a dynamic hotspot-focused strategy that involves moving locations and a facility-based strategy that does not; (b) enable comparison based on TB notifications, given that population denominators are shared across intervention arms; and (c) reduce variability across clusters due to random chance across a small number of clusters.

Each period will last four months, in order to: (a) reflect potential implementation of a hotspot-focused strategy responsive to recent notifications; (b) facilitate intervention in up to three different sets of hotspot locations per study region over the course of the study; and (c) enable implementation of each intervention in each of the 8 regions during each of the 12 calendar months (to reduce seasonal biases). Intervention periods will be separated by four-month intervention-free "washout" periods, enabling the study to be carried out by four teams (rather than eight) and thus enhancing the likelihood of fidelity to study procedures. (Each study team will be scheduled to rotate between study regions such that the team spends equal time on each of the two interventions.) Triplets will begin implementation in staggered fashion, such that two regions (one for each sequence) will initiate an intervention every four months, optimizing the feasibility of implementation (i.e., not initiating eight sites at one time).

The use of multiple crossover periods will: (a) standardize underlying populations, (b) reduce variation across arms (and thus increase study power), and (c) facilitate equitable comparison of effectiveness between two ACF/TPT strategies – without allowing either intervention to become a "victim of its own success" by differentially reducing the underlying prevalence of TB and thus the number of notifications over time. This approach involves a tradeoff, however, in that we will not be able to directly compare the two interventions, in terms of their effect on underlying TB prevalence. We mitigate this concern by comparing notification trends in the intervention regions (facility-based and hotspot-focused) combined against those in control regions. Thus, while we cannot detect a differential effect on TB prevalence across the two interventions, we will be able to

detect an intervention-versus-control effect while also identifying the intervention that resulted in the greatest increase in notifications overall.

4.3 JUSTIFICATION FOR INTERVENTION

The intervention is chosen to align with current recommendations for TB screening, and to be feasible for implementation at scale if found to be effective at increasing TB notification. In particular, the screening algorithm of X-ray followed by sputum testing is an approach that was recently recommended by WHO and that is being adopted elsewhere in Uganda. Our use of an ultra-portable chest X-ray device and setup, managed by a two- or three-person screening team, reflects the mobility and streamlined staffing that would be necessary for programmatic implementation of community-based TB screening in Uganda. The use of existing laboratory systems for confirmatory Xpert testing, and the use of TST rather than more expensive and technically complex interferon gamma release assays for TPT eligibility assessment, are based on a pragmatic approach to assessing the potential effectiveness of the interventions in a programmatic setting. The decision to link patients to routine care rather than providing treatment or TPT in a research context, and the decision to use a primary endpoint that requires linkage to care rather than only TB diagnosis, allow us to assess the interventions in light of the ultimate objective of reducing the burden of untreated prevalent TB in study communities.

4.4 END-OF-STUDY DEFINITION

Each participant's direct study participation will end when they are informed of a positive Xpert result and linked to TB care, or when those with a negative or no Xpert result are referred for TPT (e.g. after a positive TST result), are ineligible for TPT, have a negative TST result, do not complete reading after TST placement, or decline consideration of TPT. For each participant who is eligible for treatment or TPT, facility registers will also be monitored through the end of the subsequent washout period, to assess their linkage to care.

Health facilities' total (deidentified) notifications and TPT initiations will be tracked through the end of the final intervention period in the last two clusters, and the end of that intervention period will mark the end of the study.

5 CLUSTER SELECTION

5.1 CLUSTER DEFINITION

The study interventions will be allocated to "study regions" (the clusters) consisting of a central health facility and its catchment area. The facility-based intervention will be implemented on the grounds of the health facility, and the hotspot intervention will be implemented within a portion of the catchment area with a high predicted burden of TB (see Hotspot Selection below). The study region boundaries will be selected to include the residences of at

least 75% of the TB patients who are treated at each region's central health facility (see Delineation of Study Region Boundaries, below). TB notifications among residents of this study region will count toward the primary endpoint. If additional health facilities are identified in or near a study region which treat TB in a substantial number of the region's residents, then those facilities' TB registers will also be reviewed for notifications which will contribute to the primary endpoint.

5.2 CLUSTER ELIGIBILITY CRITERIA

Study regions must meet the following criteria:

- Level III or IV health center or district/regional hospital;
- Located within 200km of Kampala but outside the formal city limit;
- Annual volume of at least 35 patients with bacteriologically confirmed TB per year;
- Xpert facilities available on site;
- Facility leadership and TB clinical staff express willingness to adopt study procedures.

In addition, after delineating study region boundaries (see below), we require that all 12 study regions are non-overlapping.

5.3 DELINEATION OF STUDY REGION BOUNDARIES AND CONTRIBUTING HEALTH FACILITIES

Study regions will be defined at the subcounty level (mean population 25,000; IQR 15,000-38,000) unless health facility personnel advise that it is more appropriate to include only a portion of a given subcounty within their facility's catchment area. For each participating central health facility, we will identify a set of subcounties which are the source of at least 75% of the facility's TB patients, and whose residents would be expected to seek care for TB symptoms either at the region's central health facility or at other nearby facilities whose TB registers we can access for data abstraction.

5.4 HOTSPOT SELECTION

To reflect approaches likely to be taken in future practice, the area(s) that receive ACF/TPT during each hotspot-focused intervention period will be selected by a designated staff person (e.g., the TB Focal Person) at each study region's central health facility, starting from their own knowledge of the region, but also informed by data including recent TB notification rates which study staff will provide. The goal in hotspot selection is to identify areas with a high prevalence of undiagnosed TB that could be diagnosed through active case-finding.

Prior to the start of each hotspot-focused intervention period, study staff will estimate recent notification rates within the study region at the subcounty and parish levels, using notifications abstracted from local health

facility registers in conjunction with census-estimated population denominators. They will provide these estimates to the designated health facility personnel, along with data on the TB screening yield at any previously selected hotspots (the month-by-month number of screening participants, and the overall proportion of participants who tested positive), and (potentially) maps, parish-level socioeconomic indicators, parish-level rates of TB diagnostic testing as abstracted from health facility laboratory registers, or other available data.

The designated health facility personnel will be asked to first identify a preliminary list of parishes that are likely to have a high burden of undiagnosed TB, in consultation with colleagues and others (e.g. political leaders) who know the local area. After making an initial list, they will be presented with data compiled by the study team and asked to consider whether their list changes. Finally, they will be asked to choose and rank the parish(es) that they judge to be the best hotspot location(s) for TB case finding during the next intervention period, totaling a minimum adult population of 10,000 based on the latest available census data. They will be asked to describe that location's deciding features, including recent estimated notification rate, known longer-term TB burden, known socioeconomic or other risk factors for TB, accessibility, population density, case-finding logistics, and any other key considerations.

During each four-month intervention period, study staff may move to new locations within the selected hotspot parishes as deemed appropriate to optimize screening yield.

As a modelling exercise to inform future strategies, at the conclusion of the study we will use log-binomial regression to evaluate which prior data considered in hotspot selection (e.g. recent notification rate, socioeconomic indicators, distance from health facility, or subjective factors) were most predictive of a high prevalence of Xpert-positive TB among the people screened in the selected hotspot.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

In order to be eligible to participate in TB screening through this study, an individual must meet all of the following criteria:

1. Age ≥15 years, OR age 5-14 and a close contact of someone diagnosed with TB
2. Provision of oral informed consent, or, if age <18 years and not legally emancipated, oral informed assent (if age 8-17) and parental informed consent (ages 5-17) to participate in the study.
3. Ability to communicate with study staff in English or Luganda, or availability of a capable interpreter who is acceptable to the participant

Individuals of all sexes and racial/ethnic groups will be eligible to participate.

6.2 EXCLUSION CRITERIA

Individuals who are on treatment for, or diagnosed with but not yet treated for, active TB at the time of screening will be excluded from participation in this study.

Individuals who reside outside of a study region will not be excluded from participation in the TB screening intervention, but they will not count toward the primary effectiveness endpoint.

6.3 SCREEN FAILURES

Patients who are determined to be ineligible for TB screening after they consent will be considered screen failures and excluded from analysis of implementation outcomes and cascades of care. These may include participants who initially provide information that would make them eligible, but who later reveal their age to be <15, withdraw consent, or reveal themselves to be on treatment after they have consented.

Because the primary outcome is defined on a cluster level and is based on notifications at the health facility (regardless of whether the notified patients would have been eligible for study interventions), screen failures will not affect the primary outcome.

6.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Apart from limiting enrollment to individuals age 15 years and older, our study intentionally has few eligibility criteria, and therefore we anticipate that most people who express interest in participating will be eligible to participate (with the rare exception of “screen failures” below). Thus, “screening” in our study protocol below refers to screening for TB (the first step after consenting to participate) rather than screening for study eligibility.

We estimate that at least one study intervention will be able to screen approximately 20 people for TB per day, or 5000 people per year (assuming 250 screening days per year). Since each cluster will perform screening for two years (one year in each intervention), we anticipate that our eight study clusters will screen a total of 80,000 individuals for TB (fewer if one intervention is less effective at recruitment) over the course of the study.

Based on the demographics of Uganda, we anticipate that women will comprise approximately 50% of the overall study sample, and Black Africans >99%. We will enroll eligible children (adolescents) between the ages of 15 and 18 if both they and their parent/guardian agree to their participation, and we will enroll adults of all ages (with no upper limit). We have chosen 15 years as the minimum age for TB screening because this is the approximate age at which TB incidence begins to rise and at which TB becomes more likely to manifest as infectious pulmonary disease. Despite this age restriction on screening participants, our primary outcome – the total number of people who start treatment for microbiologically confirmed TB (not restricted to those tested by our intervention) – will include all people diagnosed with TB, regardless of age – in order to capture the overall impact of our intervention

on TB diagnoses, including, for example, children who may be diagnosed with TB through contact investigation after an adult family member is found to have TB.

Recruitment will be based at the individual screening sites, each of which will be coordinated by a team of at least two people. At the start of the study and at the start of each intervention period for both arms, the screening team will advertise the availability of TB screening by moving through the community announcing the availability of screening and by engaging local community health workers and political leaders. On an ongoing basis during each intervention, adults and adolescents who pass by the screening center will be informed about the purpose of the study and asked if they are willing to be tested for TB. Music and/or a megaphone may be used to help draw attention and communicate the availability of TB screening.

In the facility-based arm, the ACF/TPT center will be placed in an open area within or immediately adjacent to the health facility enclosure. Study staff (when not actively screening participants) will work with clinic staff to directly recruit patients or their accompanying friends/family as they enter the facility or sit in waiting areas. Additionally, staff at the clinic will be asked to refer any patient who is willing to be screened for TB to the screening unit. Participants will be recruited regardless of TB symptoms.

For the hotspot-focused arm, by visiting each selected parish and talking with community leadership, study staff will identify an accessible area(s) for ACF/TPT center placement. When not actively screening participants, they will attempt to recruit participants from nearby public locations. If participation wanes over the course of the four-month period, the study team will visit other community locations to announce their presence and encourage participation, or will work with local political leaders and community health workers to increase word-of-mouth recruitment.

In addition, whenever participants are diagnosed with TB through our study activities, we will explain to them that their contacts are at increased risk of TB and encourage them to refer their close contacts (household contacts, and others with whom they have spent at least twelve hours cumulative in the past 3 months) for TB screening by the CHASE-TB study. For close contacts who present to our research site for screening, we will extend eligibility to ages as low as five years. (We will encourage participants with TB to refer their <5-year-old contacts directly to a health facility for evaluation.)

To improve retention, participants who require follow-up by the study (because they had an abnormal X-ray and provided sputum, or because they underwent TST placement) will be provided with a reminder card that includes a study phone number. Participants who require linkage to care due to a positive Xpert result will be contacted by telephone and, if, necessary, may be visited at their homes by a study staff member or a community health worker, to encourage them to seek TB treatment.

Most participants will not receive monetary incentives, because we do not anticipate that the national TB program would offer incentives if implementing a similar program. However, we will offer a small amount of compensation to participants who are selected for and complete the longer survey of diagnosed TB cases and selected Xpert-negative and X-ray-negative individuals, because this is done purely for research purposes. Adult and adolescent participants who complete this questionnaire (designed to last approximately 30 minutes) will be offered 10,000 Ugandan shillings (approximately 3 US dollars) for their time via mobile money (or cash if they

do not have a cellular phone) immediately after they complete the survey. For those who are diagnosed with TB, an additional 20,000 Ugandan shillings will be provide as transportation reimbursement, also via mobile money, after study staff determine that they have visited a nearby health facility to initiate treatment. Reimbursement will not be provided for initiating preventive therapy.

7 STUDY INTERVENTIONS

7.1 STUDY INTERVENTIONS

7.1.1 STUDY INTERVENTIONS

This study will compare facility-based and hotspot-focused approaches to TB active case finding and linkage to preventive therapy. Twelve clusters or study regions (of which eight will be randomized to receive interventions) will be defined according to the catchment areas of twelve participating Ugandan district hospitals/major health centers. Eight study areas will receive a total of six 4-month intervention periods (alternating between the facility-based and the hotspot focused strategy, for three periods of each type) over a four-year period, with a 4-month wash-out period after each intervention period. Four additional areas will be used as control sites; the only involvement of participants in these sites will be through retrospective collection of de-identified data.

Both interventions will utilize mobile X-ray screening, followed by confirmatory sputum testing for those with abnormal X-rays (described in detail under “Individual-level Procedures” below). Our two intervention arms are primarily distinguished by the TB screening location: For facility-based ACF/TPT, screening centers will be situated on or immediately adjacent to the grounds of the central health facility in each study region. For hotspot-focused ACF/TPT, screening centers will be deployed to community settings in a portion of the study region selected as the target “hotspot” (see Hotspot Selection above).

7.1.2 ADMINISTRATION AND INDIVIDUAL-LEVEL PROCEDURES

Administration and recruitment

A team of at least two research staff (including at least one study nurse) will carry out the intervention in each region during intervention periods. As regions alternate between intervention and washout periods, each team will move between adjacent regions, such that each team conducts screening continuously and spends an equal amount of time doing each of the two interventions. For both interventions, screening will occur approximately five days per week (including at least one weekend day per week for hotspot-focused screening) throughout the four-month intervention period, excluding holidays (which will be equally distributed across both interventions due to the scheduling of each intervention to cumulatively cover one full calendar year).

Participant enrollment and TB screening will take place in a screening station, erected inside a tent if no easily accessed covered structure already exists in the screening location. Each screening station will contain a mobile X-ray device and accompanying interpretation software, electronic tablets for data capture, supplies for TST placement and reading, supplies for sputum collection and labeling, and a portable table and chairs. For the facility-based intervention, a screening station will be set up on/near health facility grounds. When not actively screening participants, study staff will work with health facility staff to directly recruit patients (irrespective of TB symptoms) or their accompanying friends/family as they come and go or while they are sitting in waiting areas. For the hotspot-focused intervention, study staff will identify a location for screening station placement that is visible and accessible from a heavily trafficked area such as a transit hub or market, and will recruit participants by interacting with passersby, by visiting nearby homes and shops when enrollment slows, and by engaging local health workers and community leaders to help spread the word about the availability of TB screening. In both study arms, equipment will be stored and charged overnight, typically at the region's central health facility, where sputum specimens will also be delivered at the end of the day for Xpert testing.

TB screening procedures

After obtaining consent as described below, non-pregnant participants will be screened by digital chest X-ray using a portable X-ray device. (Those who are unsure of their pregnancy status will be offered urine pregnancy testing, and those who report pregnancy or are found to be pregnant will proceed directly to sputum testing. We will consider adding an allowance for sputum testing for people unable to participate in X-ray screening for other reasons, depending on our initial experience in the first two sites.) Chest X-rays will be read in real-time by the version 3 of the automated, deep-learning-based software qXR (Qure.ai). Participants with abnormal radiographs meeting the study's threshold for possible TB (see below) will proceed to sputum testing. All participants who consent to screening will also be asked to complete a brief survey.

Participants whose X-rays are read as abnormal will be asked to provide expectorated sputum samples for Xpert MTB/RIF Ultra ("Xpert") testing to confirm TB disease, and contact information for follow-up of results; if unable to expectorate after coaching by study staff, they will be referred to the clinic for further management with a written description of their X-ray findings (and a digital copy when possible). Xpert testing will be performed at the nearest available testing facility – typically the central health facility in the study region. Participants who undergo Xpert will be advised to return after a specified time window (typically 2-7 days) for their result. For those with positive results who do not return, study staff will attempt to contact them via telephone or in-person visit (potentially with support of a local community health worker).

All individuals with positive Xpert results will be provided with written documentation of their chest X-ray and Xpert results and referred to the corresponding health facility for management – including initiation of anti-TB treatment where indicated – under the guidance of a (non-study) clinician. Other groups of individuals will be referred to a nearby TB diagnostic and treatment facility for further evaluation and consideration of TB treatment: Individuals with negative Xpert results but both symptoms and x-ray findings concerning for TB, individuals with X-ray and symptoms suggestive of TB who are unable to produce sputum, and close contacts of a TB case who have an X-ray suggestive of TB and are unable to produce sputum. Individuals who have chest X-ray highly concerning for TB (defined by qXR score ≥0.8) will be offered a second sputum Xpert testing if the first test is

negative. Finally, because qXR is also able to identify TB-unrelated abnormal findings on X-ray, qure.ai has configured our software to identify and flag six clinically actionable non-TB abnormalities: cardiomegaly (moderate or greater), pleural effusion (moderate or greater), rib fracture, pneumothorax (moderate or greater), nodule concerning for malignancy, and lobar consolidation). Participants with these abnormalities will be provided with a written description of the findings (with study contact information to share with clinicians who wish to obtain image files) and advised to seek clinical evaluation – but no further evaluation will be done within the context of the research study.

Additional TB testing and HIV screening during the final year of the study

We will offer additional diagnostic testing for CHASE-TB participants for a period of approximately three months during the last year of the screening, simultaneously at all four active study sites. This activity will be conducted as part of a sub-study funded by NIAID. During this period, the X-ray score threshold for repeating sputum Xpert testing will be lowered to ≥0.5. Participants with X-ray scores ≥0.5 will also be offered sputum culture. Sputum culture specimens will be refrigerated and transported to the laboratory in Kampala for processing and research staff will ensure that participants' contact information is maintained and that results are communicated with participants and the health facility that performed the participants' Xpert testing.

Additionally, during this period, study staff will offer point-of-care HIV testing and counseling to all participants with X-ray scores ≥0.1 who are not known to be HIV-positive. HIV testing will also be available upon request to other participants, including pregnant women or others without abnormal chest X-ray. For participants who are either newly diagnosed with HIV through study activities or known to be HIV-positive but not receiving antiretroviral therapy, the study team will provide point-of-care urine LAM testing (for TB). All participants tested positive for HIV will be referred to a local health facility for further evaluation. We will also survey a subset of participants about their preferences for receiving HIV screening during TB screening events versus through routine clinic visits. Additionally, we will prospectively collect cost data through a review of budgets and direct observation (i.e., a time-and-motion study of study staff and participants) to document the time and resources required to conduct additional TB testing and HIV screening.

Linkage to TB Preventive Therapy (TPT)

From the start of the study until April 2024, all participants who did not have evidence of active TB (i.e. those with normal X-ray results or negative Xpert results) and who were not currently taking TB preventive therapy were considered for TPT eligibility and referral. As of April 24, 2024, consideration of TPT referral was limited to people who were close contacts of a TB or living with HIV, due to low uptake and yield among the broader participating population.

To simplify the number of interactions with study staff that are required to be linked to TPT, those with TB-presumptive x-rays will be offered TPT information and TST if eligible at the time of sputum collection, with plan to read the TST and consider TPT referral once Xpert results are available for the majority whose Xpert results will be negative. Criteria for TPT eligibility without TB infection testing will be based on current guidance from Uganda's National TB and Leprosy Program (NTLP). This guidance currently includes those who are known to be living with HIV who have not received TB treatment or TPT previously or who have a recent known TB contact;

these individuals will be provided with written documentation of their negative chest X-ray and/or Xpert results and encouraged to present to the local clinic for TPT initiation. Based on current practice in Uganda, close contacts of a sputum-positive TB case will be offered TST and referred if the test is positive, but those who are unable or unwilling to complete TST will also be referred for consideration of TPT without a TST result. Participants for whom a TST result could affect TPT eligibility will be counseled about tuberculin skin testing (TST), including indication, accuracy, the appearance of positive results, and possible side effects. After receiving this information, participants will be asked if they would like to receive a TST and would present to clinic for TPT initiation if the TST result were positive. TST will be offered only to those who express a willingness to initiate TPT if they have a positive TST result. Novel skin tests may be included as a replacement for TST if they are WHO-approved, available in Uganda, and similar in price to TST.

For eligible participants who accept TST evaluation, 0.1ml of tuberculin purified protein derivative will be injected intradermally in the flexor surface of the forearm, and participants will be asked to return to the ACF/TPT center for TST reading after 40-96 hours. Individuals with a positive TST will be provided with documentation of their study results and, once not requiring further evaluation for active TB, they will be referred to the region's health facility for initiation of TPT. To reflect likely programmatic implementation, TPT will be provided and administered through the NTLP, and all clinical decisions will be made by clinic-based (i.e., non-study) clinicians, using the regimens available in Uganda at the time of the study.

Longer surveys

A longer survey will be administered to participants with positive Xpert results. In addition, a representative sample of TB-negative individuals who presented for screening will be selected for interview: At the time of X-ray screening, participants with normal X-rays, and pregnant participants who bypass x-ray, will be randomly selected for longer interview (initially, with probability 1/30), and those with abnormal X-rays who require Xpert testing will be randomly sampled at a higher probability (initially set at 1/15, reduced to 1/10 on 19 Sept 2022 based on lower than expected frequency of abnormal x-rays). These sampling fractions are chosen so that the expected numbers of X-ray-negative participants and of X-ray-positive but Xpert-negative participants are at least as great as the average number of Xpert-positive participants; they may be adjusted if participation rates or chest X-ray specificity differ from expectations.

Those selected at the time of normal or abnormal X-ray result will be asked to complete the longer interview before leaving the screening site (but may schedule for a later time if they prefer). Those who receive a positive Xpert result who have not already completed the longer interview will be asked to return to the screening site for the interview or complete the interview by telephone. Participants who complete the longer interview will be compensated for their time as described below. The questionnaire is designed to last approximately 30 minutes and including questions on the following topics:

- Socioeconomic status, including assessment of food insecurity;
- Access to health care, broadly and in relation to any current TB symptoms;
- Preferences for TB screening and treatment, and subjective experience of study interventions;
- Medical history and comorbidities, include any history of TB treatment or preventive therapy.

In addition, given an early observation of low rates of completion of TST reading, a consecutive sample of participants who accepted TST evaluation will be selected for a follow-up survey to assess barriers and facilitators to returning for the TST reading. During the time of recruitment for this follow-up survey (which is anticipated to last a few months), all participants who accepted TST placement but did not return promptly for TST reading will be contacted by phone before their window for TST reading closes. These participants will be asked a similar series of questions regarding the barriers they face to having their TST read.

Furthermore, we wish to understand the outcomes of clinical referrals made by the study team, and the TB incidence associated with TB-suggestive x-rays in individuals who were asymptomatic and sputum Xpert-negative at the time of screening. To accomplish the first of these objectives, a consecutive sample of participants who were referred for further clinical evaluation based on abnormal X-ray findings (either those with high concern for TB despite lack of Xpert confirmation, or abnormal TB-unrelated findings) will be contacted by study staff by telephone a few weeks after their screening, to understand and document the outcome of those referrals. During the call, participants will be asked whether they sought medical care, and if so, to describe the outcome of any further evaluation. For the second objective, individuals who had X-rays concerning for TB (regardless of whether they were diagnosed with TB through study participation) will be contacted by the study team by telephone approximately one year later to gather data about TB diagnoses and treatments. These participants will be asked whether they have been diagnosed with TB, treated for TB, and/or prescribed TPT since their participation in the study's screening activities.

Review of TB registers

TB registers at each study region's main health facility, and records of study area residents at any other facilities within the study region that diagnose or treat TB patients, will be reviewed at least every four months. Data will be abstracted from the registers to assess the primary and secondary effectiveness endpoints, identify current hotspots, and characterize the facility's diagnostic and treatment cascades:

- Treatment registers (people initiating TB treatment): name (for identification of study participants only, will be removed after linkage), age, sex, village of residence, bacteriologic test results, month of treatment initiation, treatment outcome (if available), and number of treatment visits.
- TPT registers (people initiating TPT): name (removed after linkage to study records), age, sex, parish of residence, TB risk factors, dates of TPT initiation and completions, and adherence indicators.
- Presumptive registers (people evaluated for TB): tally of number of people evaluated each month at the study area's main health facility
- Laboratory registers (specimens tested for TB at the facility): tally of Xpert tests performed each month at the study area's main health facility

Names, dates, and other identifying information will be removed after identifying screening participants and calculating intervals and aggregate measures.

7.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will occur at the cluster level. Before randomization can occur, a total of 12 clusters with suitable characteristics will be identified (see Cluster Selection, above), and the leadership at the main health facility of each cluster will agree to participate in the study. The clusters will be grouped into groups of three ("triplets") based on similar characteristics. The grouping of clusters into triplets will be stratified by the study statistician to minimize the differences among triplets with respect to the baseline covariates 1) total notifications from the study region in the previous year, 2) population size, and 3) geographic region. Then, within each triplet, one of the three clusters will be randomly assigned to control status. Of the two remaining clusters in each triplet, one will be randomly assigned to the intervention sequence ABABAB, and the other to sequence BABABA. The intervention clusters from each triplet will be assigned to one of four positions in the intervention start sequence (i.e., its first intervention period will be period 1, 2, 3, or 4 of the study). The study statistician will generate all acceptable combinations (triplets, intervention clusters and start times). Then, during a public ceremony with representatives from participating health facilities and communities, one combination will be picked.

Besides stratification and randomization, our study schema is designed to minimize temporal and seasonal bias by balancing the number of clusters performing each intervention during any given intervention period, and by scheduling the interventions in four-month blocks such that each cluster receives each intervention once during each part of the year. To minimize personnel-related bias, each screening staff member will spend an equal amount of time on each intervention.

Because the two interventions take place in obviously distinguishable locations, it is not possible to blind the study staff who will conduct the interventions or the individual study participants. Similarly, because the principal investigators will be involved in management of site-level logistics, they will not be blinded to which cluster is assigned to which intervention sequence. However, the principal investigators and statistician will be blinded to the primary outcome, which will be measured using notification data from health facility TB registers. Facility names and other location identifiers, as well as any indicators of current intervention assignment, will be removed from data extracted from TB registers by study coordinators and data managers, before they are shared with the PIs or statistician.

Details of any unblinding will be reported to the Data and Safety Monitoring Board (DSMB) and discussed, if deemed to be relevant, when reporting trial results.

8 STUDY INTERVENTION DISCONTINUATION

8.1 INDIVIDUAL-LEVEL DISCONTINUATION OF STUDY INTERVENTION

The trial's primary outcomes will be measured at the cluster level (i.e., by counting TB notifications and TST initiations, in deidentified fashion) rather than at the individual level. There are, however, implementation-related outcomes and secondary effectiveness that are based on individuals' completion of study procedures (chest X-ray, sputum testing, TST) or that rely on individuals' consent to collection and analysis of identifiable data.

Participants may choose to discontinue study procedures at any time. If participants choose not to complete all recommended procedures, but do not withdraw consent for study participation, then they will still be included in all individual-level analysis (e.g. of study reach, cascades of care, and radiographic characteristics), and the local health facility registers will still be reviewed to determine whether they have started treatment or TPT.

Participants who do not initially complete all study procedures, but who return during the same intervention period and wish to continue, may do so. Participants with a previously abnormal chest X-ray who had not completed sputum testing will be offered sputum testing without repeating the chest X-ray, regardless of the time interval. Individuals who wish to undergo repeat TB screening will be consented again for the full study intervention. Participants will be informed before TST placement that if they do not return for TST reading within 96 hours, repeat TST will not be offered.

8.2 INDIVIDUAL-LEVEL DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Because of the study's pragmatic nature and broad inclusion criteria, no investigator-led discontinuations are anticipated, but a participant may be removed if they are determined after enrollment to be ineligible (e.g. due to misreported age of a child). These individuals will be counted in certain implementation outcomes (e.g. number of X-rays performed per day) but will otherwise be excluded from analysis.
Participants are free to withdraw from participation in the study at any time upon request.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Screening Participant Case Report Form.

8.3 CLUSTER-LEVEL STUDY DISCONTINUATION

If a cluster is discontinued from the study for any reason, we will endeavor to assign a replacement cluster that meets the same eligibility criteria as the initial cluster. If this occurs within the first eight months of the study (i.e., within the first study period and washout), the replacement cluster will be assigned one additional study period at the end of the study (to balance the number of periods in each arm) and will contribute to the primary outcome instead of the initial cluster. If this occurs after the first eight months, the replacement cluster will undergo all procedures assigned to the primary cluster and will contribute to secondary outcomes but will not contribute data to the primary outcome. In this case, all analyses (including the primary analysis) will be adjusted for any imbalance in study follow-up across the arms resulting from the discontinuation of the initial cluster, but the initial cluster will be used for the primary analysis. If a cluster is discontinued in the final year of the study, no replacement cluster will be assigned.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 INDIVIDUAL PARTICIPANT ASSESSMENTS

Radiographic TB screening – A single posteroanterior chest X-ray will be digitally captured and reviewed by qXR software. Initially, a threshold qXR TB score of 0.5 was used in both intervention arms for determining which participants should undergo confirmatory sputum testing. After the first ~1000 participants, data were reviewed and the threshold was reevaluated in consultation with the DSMB, from the perspective of maximizing TB detection on a fixed screening budget. Based on the small proportion of participants with scores between 0.2 and 0.8, and the relatively high TB yield (~10% prevalence) among those with scores near 0.5, the threshold for confirmatory testing was lowered to 0.2 on 23 July 2022 to facilitate additional data collection and threshold optimization. Based on further review with the DSMB in October 2022, the TB yield remained ~10% at scores as low as 0.2-0.3, so the threshold was lowered further (to 0.1) for additional data collection as long as the Xpert testing capacity allowed.

Xpert confirmatory testing: Individuals with any positive Xpert result (including trace) in the context of a known abnormal X-ray will be referred for active TB treatment.

Tuberculin skin testing: TSTs will be read between 40 and 96 hours after placement. For HIV-negative children and adults (and assuming no change in Ugandan guidelines), induration of >10mm diameter will be defined as a positive result and will be considered an indication for TPT.

9.2 PRIMARY ENDPOINT ASSESSMENT

The primary endpoint will be assessed using data abstracted from the TB registers of the pre-identified facilities that provide TB treatment to residents of each study region. For facilities using the standard Ugandan NTLP TB Register format as of 2021, TB notifications will count toward the primary endpoint if:

(1) The notification was initially registered at that facility (i.e., it was not a “transfer in”).
(2) The registration date falls between the start of the intervention period and a date one week after the end of the intervention period. (If no registration date is recorded, then the Date Started Treatment, the first date of Issue of Anti-TB Drugs, or the Date Transferred to 2nd Line Treatment, may be used to estimate the notification date.)
(3) The patient is classified as PBC (pulmonary bacteriologically confirmed) or has documentation of pulmonary disease and bacteriologic confirmation (e.g., a positive sputum Xpert, smear microscopy, or culture result; or a positive urine LAM combined with an abnormal chest radiograph or other evidence of pulmonary involvement).
(4) The patient’s subcounty of residence is within the study area boundaries. (If the subcounty is missing from the register, then the study staff performing abstraction will attempt to determine the correct subcounty based on the listed zone, parish, and/or district, but patients will be excluded from analysis if their residence within a study area subcounty cannot be determined with reasonable certainty.)
(5) The patient type is recorded as New, Relapse, or Treatment History Unknown, or is missing (i.e., the patient is not documented as “Treatment after Failure” or “Treatment after Loss to Follow up”).

(6) The patient started treatment or was referred elsewhere for 2nd-line treatment (if drug resistant and treatment not offered locally). This criterion may be reconsidered based on a review, in early abstracted data, of whether this can be determined reliably (e.g. from documented treatment start dates or drug administration dates) and whether there are a nonnegligible number of patients who were documented as notifications but did not start treatment.

Equivalent fields will be used if register formats are updated during the study.

9.3 SECONDARY EFFECTIVENESS ASSESSMENTS

Similar to the assessment of treatment initiations, TPT initiations will be assessed using a standard, NTLP-provided TPT register. TPT initiations will count toward the secondary endpoint of TPT initiation if:

(1) A TPT initiation date is recorded and falls between the start of the intervention period and one week after the end of the intervention period; and
(2) The listed address is within the study area boundaries, or the patient is determined to reside within study boundaries as for the primary outcome above.

Secondary effectiveness endpoints related to treatment initiation will be assessed as for the primary endpoint, but omitting certain criteria (e.g. residence within the study area, date within an intervention period) or adding certain criteria (e.g. documented sex, or being a study participant) as appropriate to the specific analysis.

9.4 IMPLEMENTATION AND COST ASSESSMENTS

During routine site visits, fidelity to study procedures will be assessed using a standardized checklist. Study staff will also track implementation failures (e.g., power outages, equipment failures, lost specimens/results), and we will periodically document strain on existing systems including Xpert capacity and drug supply, for purposes of informing national decision-makers regarding future programmatic requirements for implementation.

We will conduct an empirical costing and associated cost-effectiveness analysis of the two interventions from the societal perspective. We will train a costing team to collect these costs at regular (for budgetary reviews) or randomly selected (for direct observation) times. We will measure costs prospectively and comprehensively, including those costs borne by both health systems and patients. Health systems costs will be captured using an "ingredients" approach through a combination of budgetary review, interviews of study staff, direct observation (e.g., time-and-motion studies of study staff), and prospective logbooks kept by study staff to document the time and resources required to design, initiate, and maintain the intervention in each community. Patient-level costs will be assessed via interview, integrated into the surveys described above, as well as time-and-motion observation. We will also include other societal costs, including burden on the routine healthcare system, disruption of any activities at clinics or in hotspot-focused venues, lost wages, security requirements, and costs to caregivers. Costs from this "ingredients" approach will be compared (as a check) to a "top-down" approach in which we divide large cost items (e.g., annual staff salaries) by the number of new TB cases identified and starting treatment under each strategy. For budget impact analysis, we will also estimate the eligible population

size, the number screened for TB before and after introducing each intervention, and any expected effects on TB-related costs.

9.5 UNANTICIPATED PROBLEMS

9.5.1 DEFINITION OF UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS ("UPIRSO")

An event is considered an UPIRSO when it meets all of the following criteria:

(1) It is **unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the population being studied;
Unexpected events could be either medical or non-medical events.
(2) It is **related** or **possibly related** to participation in the research (i.e. there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
and,
(3) It places subjects or others [e.g. study team members or relatives of a subject] at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.5.2 REPORTING

Research staff will be asked to report any protocol deviations to the study coordinator, who will be responsible for documenting them and reporting them to the principal investigator(s) (PI) within one week, except in cases where the deviation may have resulted in harm to a participant, in which case they should be reported to the PI immediately. Deviations will be evaluated based on their potential to harm participants and their potential to compromise the quality or integrity of research findings. Whenever potentially harmful deviations occur, or deviations occur repeatedly, a root cause analysis will be performed, and staff will be retrained or other changes implemented as appropriate.

Research staff will also be required to promptly report any unanticipated problems to the study coordinator and/or site PI, who will be expected to promptly notify the study PI. Notification of the study PI will be required on the same day if it is possible that the event constitutes a serious adverse event or an unanticipated (in terms of nature, severity, or frequency) adverse event resulting from study procedures; otherwise, notification will be expected to occur within one week.

The PI will review such events to determine whether they constitute a reportable UPRISO. Such events will be reported to the National Health Lung and Blood Institute (NHLBI), DSMB, and reviewing Institutional Review Boards (IRBs) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. Any events that are not otherwise reportable but result in protocol modifications will be reported to the IRB along with the proposed protocol amendment.

The UPIRSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number and grant number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

We will compare hotspot-focused ACF/TPT to facility-based ACF/TPT, in terms of the number of residents of the study region notified as initiating treatment for bacteriologically-confirmed new or relapsed pulmonary TB during intervention periods. The null hypothesis is that there will be no difference in this primary endpoint between the two arms.

- Secondary Endpoint(s):

1. As secondary effectiveness outcomes, we will test whether:

a. There is a difference between Hotspot-focused ACF/TPT and facility-based TPT, in terms of the number of study region residents initiating TB preventive therapy during intervention periods.

b. Compared to control regions which receive no ACF/TPT for the duration of the study, more residents will be notified as initiating treatment for bacteriologically-confirmed new or relapsed pulmonary TB over the course of the study in study regions which receive hotspot-focused and facility-based ACF/TPT interventions.

c. The TB notification rate will decline more rapidly (or increase less rapidly) in clusters which received the intervention than in control clusters.

d. There is a difference between hotspot-focused and facility-based ACF/TPT, in terms of the number of people who are diagnosed with TB through study participation and initiate treatment for TB during intervention periods.

2. As implementation outcomes, we will test whether there is a difference between hotspot-focused and facility-based ACF/TPT in terms of:

a. the total number of people screened for TB,

b. the number of people identified with Xpert-positive sputum,

c. the number of identified TB contacts screened for TB

We will also evaluate completion of each step of the care cascades (including TST, linkage to care) and compare the above effectiveness and implementation outcomes in specified subgroups (age, sex, HIV status, contact status, residence), as described in tertiary endpoints above.

Additional cost-effectiveness outcomes will include evaluating whether:

d. The more effective ACF/TPT intervention will be cost-effective relative to the less effective intervention, in terms of cost per disability-adjusted life year averted being less than country-specific cost-effectiveness thresholds,

e. ACF/TPT (either hotspot-focused or facility-based) will be cost-effective relative to no screening, in terms of cost per disability-adjusted life year averted being less than country-specific cost-effectiveness thresholds.

10.2 SAMPLE SIZE DETERMINATION

Primary outcome, statistical method, and hypotheses

Sample size is based on power to identify a difference in number of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing periods in which regions performed hotspot-focused ACF/TPT to those in which facility-based ACF/TPT was performed. Our trial will generate a count of this primary outcome in each of the 8 clusters during each of the four-month intervention periods. We conducted a simulation study to determine power under various parameter assumptions.

Expected effect size

In an initial survey, eligible primary health facilities notified mean 91 bacteriologically confirmed pulmonary TB cases (standard deviation 42) in 2020. The primary outcome we measure will reflect a sum of these routine notifications (potentially adjusted to remove notifications from cluster non-residents but add cluster residents who were diagnosed at another nearby facility) plus the incremental yield of our study interventions.

We estimate that the more effective study intervention will be able to screen 5000 people per cluster over a total of twelve months (three 4-month periods) assigned to that intervention; this corresponds to approximately 20 people per screening day.[34,35] We also estimate that this screening will lead to TB diagnosis and treatment initiation for 1.5% of participants,[21] resulting in approximately 80 cases identified per cluster per year (26.7 per four-month intervention period). These will largely be diagnoses made in addition to the 90 per cluster per year

identified through routine care (thus resulting in a total of 170 cases diagnosed per year during the intervention periods).

We consider a minimum clinically important difference to be a difference of 30 cases diagnosed between the two interventions per study region per year (e.g., 80 versus 50 incremental cases diagnosed by the study interventions, or 170 versus 140 total notifications when added to a baseline of 90 routine notifications). We believe that, if the difference in the number of cases diagnosed between the two interventions is fewer than 30 cases per region per year, the cheaper and more feasible intervention (likely facility-based ACF/TPT) would be preferred programmatically.

Our sample size is chosen to provide power of 90% to detect an effect of this magnitude, with a type I error rate (alpha) of 0.05.

Power estimate simulation

Due to the nature of our study design , the need to account for the expected overdispersion in our data, and the underlying mechanisms (i.e., both routine diagnoses and additional diagnoses made by the study) that we expect to contribute to our primary outcome, we developed a custom simulation model in R statistical software, with the following elements and assumptions:

- We simulated eight intervention clusters, each with an underlying (unobserved) rate of routine TB notification at the start of the study. These underlying rates were drawn randomly from a negative binomial distribution with a mean value of 90 cases per year and overdispersion factor mu^2/(var - mu) = 5 (R package MASS::rnegbin).

- Using these rates, we simulated the number of routine notifications in each four-month period, in absence of the intervention, starting one year before the study and continuing throughout the duration of the study. Based on trends in Uganda's TB notifications over time (prior to the COVID-19 pandemic), each cluster's underlying notification rate was assumed to decline at 3% per year from its initial value (varied in sensitivity analysis). The number of notifications in each four-month period was drawn randomly from a negative binomial distribution, with a mean equal to the expected notifications per four month period (dividing the annual rate by three, after incorporating the 3%/year decline), and with a small amount of overdispersion (overdispersion factor of mu^2/(var - mu) = 50, varied in sensitivity analysis).

- We randomly assigned each cluster to a study arm. In order to improve efficiency and obtain reasonable balance in the two study arms, clusters were first paired based on the observed notifications in the year prior to the study. Then, within each pair, one cluster was randomly assigned to sequence ABABAB and the other to BABABA.

- We simulated the additional notifications generated by each intervention. For our primary estimates of power (Table 1 below), we modeled the notifications generated by each intervention as uncorrelated with the underlying routine notification rate in the same study region. (Thus, for example, a low existing notification rate could represent either a low underlying prevalence of TB [and thus low expected additional diagnoses from the

intervention] or a weak healthcare infrastructure [and thus high expected additional diagnoses].) We assumed that the more effective intervention generated incremental diagnoses at a given mean rate (e.g., 80 per year), and the less effective intervention generated incremental diagnoses at a lower mean rate (e.g., 50 per year = difference of 30 per year between interventions). The actual number of incremental diagnoses in each four-month period, in each region, was simulated as a random draw from a negative binomial distribution with an intervention-specific mean (e.g., 80/3 or 50/3 per four-month period) and an overdispersion factor of 10 across clusters and periods (i.e., half as much excess variance as observed in the routine notification rate across clusters; varied in sensitivity analysis). In a secondary simulation, we assumed the number of incremental notifications generated by an intervention in each region varied in proportion to the underlying routine notification rate in the same region (while still assuming the same mean rates as for the primary simulation, e.g., 80 versus 50 incremental notifications, in a region with an average background notification rate). In both simulations, these incremental notifications were added to the simulated routine notifications for each cluster period.

- In analyzing the resulting data, the matching was broken. The data were analyzed using a negative binomial mixed effects regression model with fixed effects for intervention and period and random effects for cluster (R function glmer.nb). When this model did not converge for a simulated dataset, we evaluated power by log-transforming the outcome (number of notifications) and applying the t-test accounting for clustering. The t-test has been demonstrated to be robust in the case of small numbers of clusters.

- For each combination of intervention effect sizes and other assumptions, the trial was simulated 1000 times. We estimated study power as the proportion of simulations that resulted in identification of the more effective intervention with a two-sided p-value <0.05.

As a final check, we compared our power estimates with those of an existing power calculator for cluster-randomized crossover trials (Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J Epidemiol. 2020 Feb 22) for a multiple-period cross-over trial with a count outcome and cluster size of 1 (single count measurement per cluster period). Our power estimates were broadly consistent with those generated by this calculator. We also consulted with the authors of the power calculator to confirm the appropriate incorporation of our assumptions (e.g., primary outcome modeled as a count).

Our trial simulation resulted in the following estimates of power:

Table 1: Primary power estimates (simulating independent notification yields of routine and active case finding):

		Mean annual cases per cluster detected during intervention periods for more effective intervention*			
		130	150	170	190
Difference, more vs less effective intervention	10	40%	30%	25%	21%
	20	85%	78%	65%	55%
	30	99%	96%	**93%**	87%
	40	>99%	>99%	99%	98%

* Includes average of 90 notifications/cluster/year without ACF. Thus, a primary estimate of 80 incremental cases detected by the more effective intervention corresponds 170 total annual cases per cluster (with a minimum important difference of 30, bold, if the less effective intervention detects 50 incremental cases).

We therefore estimate that our trial, as designed, has 93% power to detect a minimum clinically important difference of 30 notifications per region per year, comparing hotspot-focused to facility-based ACF/TPT. This estimate is relatively robust to the number of routine diagnoses made, remaining above 87% as long as the difference between arms is at least 30 notifications per region per year. If fewer diagnoses are made through the routine system (left-hand columns of **Table 1**), our power increases. If some of the people diagnosed through an intervention reside outside of the study region, then they will not be counted toward the primary outcome, and thus the incremental effect of that intervention will be reduced; this will be assessed in secondary implementation outcomes.

Our primary estimate of power falls from 93% to 91% (**Table 2**) if we assume strong correlation between the underlying notification rate and the additional rate of notifications generated by our intervention (e.g., if there are more cases of undiagnosed prevalent TB in regions that also have higher rates of routine diagnoses). If the level of overdispersion within clusters (e.g., variation in notifications, comparing Jan-Apr 2023 to Jan-Apr 2024 in the same region) is higher than anticipated, our power falls (**Table 3**) – but we will still have 90% power to detect an incremental difference of 40 cases per region per year.

Table 2: Power estimates assuming correlation between a cluster's routine notification rate and the incremental cases identified through active case finding in the cluster

		Mean annual cases per cluster detected during intervention periods for more effective intervention			
		130	150	170	190
Difference, more vs less effective intervention	10	35%	30%	23%	19%
	20	82%	68%	57%	52%
	30	99%	97%	**91%**	84%
	40	>99%	>99%	99%	97%

Table 3: Sensitivity analysis with greater overdispersion within clusters (overdispersion factor = 5 for routine and intervention notifications across clusters and periods):

		Mean annual cases per cluster detected during intervention periods for more effective intervention			
		130	150	170	190
Difference, more vs less effective intervention	10	22%	20%	14%	13%
	20	52%	43%	36%	32%
	30	80%	73%	**64%**	55%
	40	93%	92%	90%	83%

Secondary outcomes

We also estimated our power for the secondary effectiveness outcome of TB notifications, comparing interventions to control.

In general, we anticipate substantially greater power for the intervention-to-control comparison than for the hotspot-versus-facility comparison, as we expect that either intervention will result in a large number of notifications that will not be seen in the control regions. However, it is possible that the interventions also reduce the prevalence of TB over time in the intervention periods – an effect that we will evaluate separately, but that might dilute this comparison. Thus, we perform power calculations that also incorporate this effect.

For this comparison, we use the same TB notification outcome as for the primary analysis. Our comparison is between notifications generated in regions where a study intervention was being implemented, and notifications in control regions during the same period. This comparison is similar to the primary comparison, but with a fully parallel (rather than crossover) design comparing the eight intervention regions to the four control regions. Like for the primary comparison, these data will be analyzed using a negative binomial mixed effects model with random effects for clusters (regions) and fixed effects for periods. However, for this analysis, we assume that the intervention is effective in reducing TB prevalence over time – such that the number of notifications in intervention regions falls more rapidly (counting "against" the intervention) than in control regions.

Assuming the same distribution of routine notification rates across clusters as above, and assuming that the intervention causes baseline notifications to decline at a greater rate than in control clusters (6% versus 3% per year), we expect >80% power to detect a difference between one intervention arm and the standard of care if the intervention increases notifications in an average study region by 60 cases per year from current levels (**Table 4**). We will also compare the interventions to the standard of care in aggregate; if both interventions increase notifications, then our power to detect a difference between the aggregated interventions and the standard of care will be higher than the estimates shown in the table.

Table 4: Power to detect a difference between one ACF/TPT intervention and standard of care, at α=0.05

		Mean annual cases per cluster detected during intervention			
		110	130	150	170
Mean annual notifications per control cluster at start of study	70	66%	95%	98%	>99%
	90	<10%	43%	**82%**	96%
	110	NA	<10%	27%	66%

10.3 POPULATIONS FOR ANALYSES

The primary analysis of this cluster-randomized trial will include all residents initiated on treatment for pulmonary bacteriologically confirmed TB in the corresponding study region during a 4-month intervention period (or in the one week immediately after). All residents initiated on treatment will be counted regardless of whether they were diagnosed directly through study activities or through routine care. This analysis minimizes the risk of bias (e.g., individuals who may have been sensitized through the intervention but sought care at the local health facility instead), and maximizes relevance to programmatic implementation. We will make no exclusions on the basis of age, prior TB treatment, or microbiological test used for confirmation – but to avoid including false-positive diagnoses made as a result of our ACF activities, we will exclude diagnoses that were made on the basis of clinical judgment or X-ray findings alone. In addition, we will count only notifications of TB treatment for individuals whose residence, as documented in the TB register, is within the predefined study region. To ensure as complete a count as possible of TB notifications among study region residents, we will collect treatment data not only from the cluster's primary facility but also from any other facilities that we identify as generating TB notifications within a study region. To allow time for linkage to care for cases found at the end of an intervention period, but to dilute effects as little as possible, we will count TB notifications toward our primary outcome if the patients both are notified within and initiate treatment within a time period that includes the full four-month intervention period and one week beyond the intervention period end date.

We will also perform secondary analyses of this endpoint which limit analysis to enrolled study participants (roughly equivalent to a per protocol analysis) or which remove restrictions on residence or type of TB diagnosis.

Study regions and a list of their component subcounties, parishes, and villages will be defined prior to the start of the study, as will the list of additional health facilities from which TB notification data will be collected for each study region. Study region delineations will be updated only if changes to political boundaries (e.g. splitting or merging of villages) occur during the study, and health facilities will be added or removed only if changes in available health services (e.g. introduction of molecular diagnostic capacity) substantially alter the proportion of study area residents who are treated for TB at those facilities.

10.4 STATISTICAL ANALYSES

10.4.1 GENERAL APPROACH

This is a cluster-randomized, multiple period crossover trial with no-intervention control clusters. Effectiveness analyses will be performed with a two-sided type I error rate of 0.05.

Effectiveness outcomes will be measured as a difference in raw numbers of notifications or TPT initiations between two arms, and will be expressed as a mean and 95% confidence interval per study region per four-month intervention period.

Other secondary outcomes will be reported according to the appropriate summary statistics, e.g.

- Percentages and proportions for categorical data, with display of the denominator (e.g. number of subjects with non-missing data).
- Mean, median, and range for continuous data.
- Median and 95% uncertainty range across a Bayesian posterior, for modeling results.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The trial's primary outcome measure is a cluster-level count of residents initiated on TB treatment in each of the 8 clusters during each of the four-month intervention periods.

We expect high variance between clusters, and we will analyze these data using a negative binomial regression model with robust standard errors to account for clustering, and fixed effects for periods.

Results will be presented as a "treatment initiation ratio", a ratio of the number of TB treatment initiations in the hotspot-focused versus facility-based ACF/TPT arm, with the corresponding 95% confidence interval.

10.4.3 ANALYSIS OF SELECTED SECONDARY AND TERTIARY ENDPOINTS

Like the primary endpoint, TPT initiations among study region residents will be counted with stratification by intervention period and by study region with a one-week allowance beyond the end of each period for linkage to care. Counts will be compared between the two interventions using a negative binomial mixed effects regression model with random effects for clusters and fixed effects for periods. Analysis will be stratified before/after April 24, 2024, when we restricted TPT referral eligibility to contacts and people with HIV.

Comparison of primary TB-notification endpoint, between interventions and no intervention:

If one intervention is determined to be more effective than the other per the primary endpoint, then the primary TB notification endpoint will be compared between the more effective intervention and control clusters receiving no intervention. Regardless of the finding of the primary endpoint, the two interventions will also be compared in aggregate to no intervention. For each of these comparisons, we will count notifications from control clusters in

the same manner as for intervention clusters (using periods of 4 months plus one week for each intervention period, but generating a count for every intervention period in every control cluster because there are no crossovers or washout periods). We will then compare intervention to control using a negative binomial regression model with robust standard errors and fixed effects for periods, as for the primary endpoint.

Implementation endpoints

Given the clustered nature of the data, we will use generalized linear mixed models to compare the reach of study interventions in terms of the number of people screened, the number testing Xpert positive (i.e., the number diagnosed with TB).

We will project the incremental cost-effectiveness of facility-based versus hotspot-focused ACF/TPT by constructing a Markov model of outcomes among the screening population, using a societal perspective and lifetime time horizon. Our primary cost-effectiveness outcome will be the incremental cost per disability-adjusted life year (DALY) averted, comparing hotspot-focused to facility-based ACF/TPT. An *a priori* secondary analysis will compare the more effective strategy to the standard of care. For this analysis, we will first take the empiric cost estimates described above and link them to the primary effectiveness estimate, thus generating a direct estimate of the incremental cost per person initiated on treatment for pulmonary TB – with a minimum of assumptions required. This cost-effectiveness estimate will include the full cost of intervention implementation, and we will perform scenario and sensitivity analyses to estimate how cost-effectiveness might generalize to settings of different epidemiological (e.g., TB prevalence) or economic (e.g., cost of labor) settings. We will also use our estimates of variance in both cost and effectiveness outcomes in a probabilistic uncertainty analysis to generate uncertainty ranges around this estimate of incremental cost-effectiveness. After performing this initial, trial-based cost-effectiveness analysis, we will use external data to construct a Markov model of lifetime outcomes (incident TB, TB mortality, and DALYs) in the screened population under each intervention (or the standard of care). We will then compare the incremental cost per disability-adjusted life year (DALY) averted, after incorporating data from the Ugandan TB program and the published scientific literature to construct a Markov model of lifetime outcomes (incident TB, TB mortality, and DALYs) in the screened population. Each comparison will be made between hotspot-focused and facility-based ACF/TPT and, secondarily, between the more effective strategy (as determined by our primary outcome above) to the standard of care.

Tertiary endpoints

Increases in notifications due to our ACF/TPT interventions are likely to be due to a combination of (a) diagnosing people with TB who would never otherwise be diagnosed and (b) diagnosing people early who would otherwise have been diagnosed at a later time. The latter of these effects will both increase notifications during intervention periods and reduce notifications during washout periods, compared to no intervention. To assess the combination of these two effects, we will evaluate the hypothesis that more notifications will be observed during intervention periods than during the washout periods that follow them. We will conduct negative binomial regression analyses that include data from both intervention and washout periods with fixed effects for period, and we will adjust for carryover effects as well as linear or nonlinear time effects. This analysis will enable us to evaluate if the notifications shift upwards during intervention periods versus washout periods and whether, over time, the

notifications decrease. Considering that the two interventions may draw differently from future notifications even if they do not differ on the primary endpoint, we will perform this analysis for the two interventions separately (pairing each intervention with the washout that follows it) and for both interventions in aggregate, regardless of the findings for the primary endpoint.

Estimated effects of the ACF/TPT interventions (in aggregate) on the burden of TB in the population:

We will consider trends in the number of TB notifications in a region over time as a reflection of the number of cases available to be diagnosed either through the intervention or through routine care. Although a single four-month intervention period is likely to increase notifications relative to the number that would have been diagnosed in the same period without the intervention, the repeated periods of intervention (including both TB treatment and TPT) in the same study region may, over time, decrease the number of people with TB who can be diagnosed and treated either by the intervention or through routine care. To test the hypothesis that the TB notification rate decreases more quickly over time in intervention clusters than in control clusters, we will repeat the negative binomial regression analyses with both intervention and washout periods described above, but with inclusion of control clusters. We will conduct a differences in differences analysis to compare the estimated linear time effect (as an annual rate of change in TB notifications) in intervention clusters versus control clusters over the course of the study, interpreting the difference in rates of change as the impact of the interventions on TB burden. Secondarily, we will compare the rate of change in intervention clusters to the rate of change in notification rates for Uganda as a whole during the same period. If a year of post-study notification data can be captured, we will perform a similar analysis comparing notifications in the year prior to the study to notifications in the year after the study ends, again comparing differences within intervention clusters to differences within control clusters.

10.4.4 BASELINE DESCRIPTIVE STATISTICS

Prior to randomization, clusters will be grouped into triplets with similar baseline characteristics as described above. After randomization, intervention and control groups (of 4 clusters each) will be compared based on the characteristics used for matching ((1) annual bacteriologically confirmed TB notifications from catchment residents in 2019-2021, (2) estimated population size of catchment areas, (3) proportion of notifications from the study region who are treated at the study facility, (4) hospital versus health centre facility type) and on additional baseline characteristics of (5) total number of annual TB notifications (any type) among people from the study region, (6) total annual TB notifications at the region's central health facility (regardless of patient residence), (7) annual number of TPT initiations among people from the study region, (8) proportion of notified TB patients from the study region who are diagnosed at the study facility, (9) age and sex distribution of people from the study region initiating TB treatment.

10.4.5 PLANNED INTERIM ANALYSES

There will be no interim analysis of the primary nor secondary outcomes/endpoints.

10.4.6 SUB-GROUP ANALYSES

The primary outcome is measurable only at the cluster level and with limited data about the individual patients whose TB notifications count toward the primary outcome. However, we will also analyze the primary outcome separately for notifications among men, notifications among women, and notifications among individuals >15 years old. For these subgroup analyses, only notifications among patients of a given sex as documented in the TB registers will be counted, but analyses will otherwise be performed as for the primary analysis. Similar sex subgroup analyses will be performed for the comparison of notifications between interventions and control clusters and for the comparison of TPT initiations between the two interventions.

Among secondary implementation endpoints, we will perform subgroup analyses to ascertain whether reach differs by strategy according to age (<15 [contacts only], 15-25, 25-40, >40), sex (male, female), HIV status (HIV-, HIV+ on ART, HIV+ not on ART), contact status (TB contact or not a known contact), and residence (within study region versus overall, and in identified hotspots versus overall). We will incorporate these variables as product ("interaction") terms in GLMM models that also include primary intervention effects, to formally evaluate whether reach and implementation differ for hotspot-focused vs facility-based ACF/TPT. For descriptions of cascades of care, comparisons of the proportion completing each step, between the two intervention arms, will be evaluated within these same pre-specified subgroups.

No subgroup analyses will be performed by race because we anticipate nearly all study participants to be Black African.

10.4.7 EXPLORATORY ANALYSES

We will explore the accuracy of our study's hotspot identification, evaluating whether the prevalence among individuals screened is higher than among facility-based screening participants, and exploring differences between the screening populations that may help us to understand reasons for lower than expected yield, e.g. differences in health care access as assessed through survey responses, evidence of delayed diagnosis through disease burden or self-reported symptom duration, or demographic characteristic of screening participants.

We will use descriptive cascade analysis to illustrate implementation of each component of the interventions and understand the steps at which yield of each intervention is most reduced.

To estimate the effect of each intervention on the extent and timing of TB diagnosis, we will develop a simulation model of TB progression and care-seeking in study regions, informed by national prevalence survey and national

and local notification data. Modeling each ACF intervention as a sampling of the population with undiagnosed prevalent TB, we will fit this model to the month-by-month numbers of TB notifications observed during the study's intervention and washout periods (recognizing that some people diagnosed through ACF would otherwise have been diagnosed during a washout period). We will use this calibrated model to estimate the increase in overall TB notifications with each intervention – which we will compare to empirical estimates from the trial itself – and the reduction in time to TB diagnosis among those diagnosed through ACF.

Finally, we will develop a transmission model to translate each intervention's effects on TB notifications, timing of diagnosis, and uptake of preventive therapy into projections of TB incidence and mortality at the population level. We anticipate that our compartmental model will include HIV and TB natural history, separation of asymptomatic and symptomatic TB, and geographic hotspots with elevated TB risk and reduced health care access, and will be calibrated to study data where possible and national-level data from Uganda otherwise, using priors informed by the literature. We will use the calibrated transmission model to project changes in TB incidence and mortality over a 10-year period, compared to continued current practice, if one of the interventions were scaled up to health facilities in the greater Kampala area for 1 to 5 years.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

Oral informed consent will be obtained from all adult participants, using a script designed to be understood by participants with limited education or health literacy. For adolescent participants (age 15 to <18 years), we will obtain parental consent and participant assent, using the same script. The script will be read to participants and made available in hard copy if desired, prior to starting the study intervention.

11.1.2 STUDY CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the funding agency and the Institutional Review Boards (IRBs) may inspect all documents and records required to be maintained by the investigator, including but not limited to, survey responses and abstracted clinical records for the participants in this study.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Johns Hopkins University. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Johns Hopkins research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Johns Hopkins University.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies:
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

11.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Johns Hopkins University. After the study is completed, the de-identified, archived data will continue to be stored for use by other researchers including those outside of the study.

No biological specimens will be stored; however, digital chest X-ray images will be included among the data to be transferred, deidentified, and stored for future use.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. However, withdrawal of consent may not be possible after the study is completed.

11.1.4 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including clinical trials, tuberculosis clinical management, and biostatistics. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least annually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NHLBI.

11.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

The study coordinator will oversee all screening teams according to a common quality management plan. Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review the documentation of the consenting process. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured in REDCap (data from participant surveys and TSTs, or abstracted from registers), laboratory source documents (Xpert tests), or qXR software (X-rays). Xpert and qXR results will ultimately be entered into the study database, and X-ray DICOM will be maintained in a separate storage folder. To ensure accuracy site staff will compare a representative sample of laboratory and X-ray source data against the database, targeting key data points in that review. A data manager will regularly query the consistency and completeness of REDCap data.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described above in "Implementation and cost assessment".

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

11.1.6 DATA HANDLING AND RECORD KEEPING

11.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Except where primary data requires another format (e.g. chest X-ray images), data will be stored in REDCap (redcap.jhu.edu). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. For laboratory reports, hard copy records will be maintained until REDCap entry has been verified by a second data clerk.

11.1.6.2 STUDY RECORDS RETENTION

Any physical study documents will be retained for a minimum period of three years from the date of Federal Financial Report (FFR) submission to NIH. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

11.1.7 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents and reported to the NHLBI Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11.1.8 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Other researchers may request data from this study after the completion of the primary endpoint by contacting the PIs or Johns Hopkins University. Considerations for ensuring confidentiality of these shared data are described in the "Study Confidentiality and Privacy" section above.

11.1.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NHLBI has established policies and procedures for all study group members (including investigators and DSMB members) to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.2 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
1.0	7 March 2022	Not applicable; this is the first version of the protocol	
1.1	9 November 2022	qXR score threshold for confirmatory testing lowered to 0.2, and as low as 0.1 as Xpert capacity allows	Relatively few participants but high TB yield for participants scoring 0.5-0.8 and 0.2-0.5.
		Identification of select high-risk incidental findings for clinical referral	Balancing clinical actionability and participant benefit with burden on participants and clinicians
		Include pregnant women in sampling for longer interview	Correction of an initial oversight
		Move timing of TST to initial encounter, for participants requiring confirmatory Xpert testing	Increase TST uptake and completion for xray-abnormal individuals who will turn out to be Xpert-negative and likely to benefit from TPT
		Limited presumptive and laboratory register data collection to monthly tallies of patient evaluations and Xpert tests	Assessments of data completeness and infeasibility of collecting parish-level care seeking rates
1.2	22 May 2023	Added details of costing activities	Finalized costing instruments prior to start of cost data collection in June 2023
		Clarified plans for classifying notifications with respect to primary outcome, including that transfers in are excluded.	Our intention is to measure impact on initial TB notifications at facilities in the study region; also avoids double-counting.
		Clarified that failure to complete TST reading also ends study participation	
		Clarified that multiple hotspots may be chosen for each round hotspot intervention period	Hotspots are selected by parish, and multiple parishes can be screened over 4 months
		Changed order of inputs to hotspot selection (local input first, then data prepared by study team)	Presenting notification rate estimates first discouraged staff from considering other knowledge about TB burden
		Modified staffing plan description (no longer based on residence or treating teams as one unit across intervention periods)	Screening staff move into a new district for each intervention period, and teams may not be fixed due to personnel changes over time

		Corrected CXR type from AP to PA	Typographical error
		Decreased allowance for linkage to care from 2 weeks to 1 week	In practice, staff are transitioning to new site during final days of 4th month, and nearly all linkage to care happens within 1 week.
1.3	23 Sept 2023	Expanded eligibility to child contacts (age 5y and above) and added relevant secondary analyses	Contacts above age 5y are high risk for TB (compared to other populations this study is targeting for screening and TPT) and do not consistently receive TPT in Uganda
		Added data collection to understand barriers to TST reading, with corresponding exploratory endpoints	Completion of TST reading was low in the first year of the study
		Added data collection to understand outcomes (result of clinical referrals, and TB incidence) in participants with abnormal x-rays, with corresponding exploratory endpoints	These groups could be additional opportunities for impact with a CXR-based TB screening intervention
1.4	25 April 2024	Limited TPT eligibility to close contacts and people with HIV, and TST to contacts only. Referred close contacts for consideration of TPT if they were TST+ or unable/unwilling to complete TST.	Low uptake and yield of TST in overall study population, so focusing on highest risk subset with greatest potential to benefit from TPT.
		Reduced qXR TB score threshold for repeat Xpert testing from 0.9 to 0.8	High (>5%) prevalence of positive second Xpert observed in qXR>0.9 group. Based on estimate of sensitivity of first Xpert and of TB prevalence in qXR 0.8-0.9 range, we anticipate this group to have ~1% of second Xperts positive, which is similar to the TB prevalence associated with our lower qXR score bound of 0.1 for initial Xpert testing.
2.0	7 October 2024	Description of longer survey information.	Previously not outlined; now includes questions related to food insecurity.
2.1	10 June 2025	Clarified eligibility for one-year follow-up calls to include people previously recommended for TB treatment	Provides another way to assess linkage to care and treatment completion
2.2	29 Oct 2025	Added additional procedures for participants with high X-ray scores during the final year of the study	Provides data on individuals with TB who were not diagnosed with single confirmatory Xpert testing.
2.3	15 May 2026	Amended to reflect a decision to end the study 8 months early. Modified notification-trend endpoint to reflect change in study timing (will also update on clinicaltrials.gov).	Due to delayed start and mid-trial funding delay, original timeline would extend beyond end of grant. Resources for completing the final 8 months are insufficient.

		Other minor corrections and clarifications (investigator contact info, qXR version and cutoff) not reflecting actual changes to procedures or analysis plans.	Accrual target of 900 Xpert-positive cases will be met by revised end date.

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