Clinic versus Hotspot Active Case Finding and Linkage to Preventive Therapy (ACF/TPT) Strategy Evaluation for TB *(CHASE-TB)*

STATISTICAL ANALYSIS PLAN

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
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Purpose

This Statistical Analysis Plan (SAP) provides the details of statistical considerations, analyses, and reports planned for the CHASE-TB study. The proposed analyses will be conducted on the entire participant sample and on pre-specified subgroups, as described in this SAP. In addition, this plan discusses statistical issues relevant to these analyses (e.g., sample data to be used, missing data, etc.).

This SAP addresses statistical analyses for primary and secondary endpoints, and for closely linked exploratory endpoints.

All data collection procedures and statistical analyses in this SAP will be finalized and approved by the CHASE-TB Study Principal Investigators (PIs) and Study Statistician. In addition, the data collection procedures and statistical analyses detailed in this SAP may be modified; however, any modifications or changes in the primary endpoint and/or its analysis will also be reflected in a protocol amendment. Any updates to the SAP will be thoroughly detailed and documented at the beginning of this document.

SAP revision history:

Version 1.0: developed during January-May 2026, based on endpoints and statistical analysis considerations originally detailed in the clinical trial protocol (available at clinicaltrials.gov).

Study Overview (duplicated from trial protocol)

Title:	Clinic versus Hotspot Active Case Finding and Linkage to Preventive Therapy (ACF/TPT) Strategy Evaluation for TB *(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:

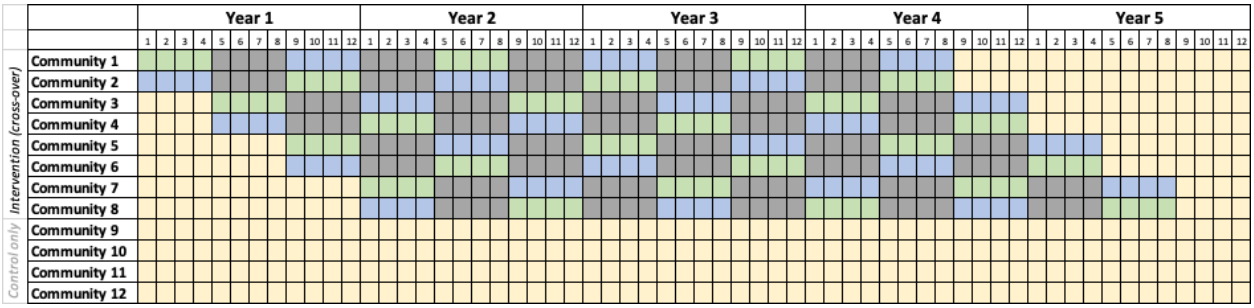
- Compare two TB active TB case-finding interventions in terms of effectiveness in increasing uptake of TPT
- Estimate impact of active TB case-finding interventions on TB treatment initiations and population TB burden, compared to no intervention
- Compare the implementation of the two interventions
- 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 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.

Full protocol:

The clinical trial protocol will be linked from clinicaltrials.gov, https://clinicaltrials.gov/study/NCT05285202.

Study size determination (excerpted from full clinical trial protocol)

The number of clusters and the number and duration of intervention periods were chosen to provide 90% power to detect a minimum clinically important 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), with a type I error rate (alpha) of 0.05, under the following assumptions:

- Routine bacteriologically confirmed pulmonary TB cases of 90 (negative binomially distributed with overdispersion factor $mu^2/(var-mu)$ of 5), based on pre-study notification data
- 5000 people screened per cluster per twelve months of screening with the more effective study intervention
- TB diagnosis and treatment initiation incremental to the background notification rate equivalent to 1.5% of participants in the more effective intervention.

Power estimates based on a trial simulation with these assumptions were:

		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).

Full power simulation details are available in the clinical trial protocol. A later update using the average screening participation rates and TB diagnostic yield observed in preliminary study data confirmed at least 80% power to detect the designated minimum clinically important effect site.

Statistical Analyses

General analysis principles

Analysis of primary and secondary effectiveness endpoints will be at a cluster level. Implementation outcomes such as reach and delivery cascades will be analyzed at an individual level.

Populations for analysis

- 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 to allow for linkage to care).
- Total screening participants.

Study region delineations were defined prior to study start and updated only if changes to political boundaries (e.g. splitting or merging of subcounties) occurred during the study.

Hypothesis testing for effectiveness will be based on a two-sided type I error rate of 0.05.

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.

Analyses will be done using Stata and R.

Table 5: Specific endpoints and corresponding analyses

OBJECTIVES	Measures	Analytical approach
Primary		
Primary objective: Compare two active TB case-finding interventions in terms of effectiveness at increasing TB diagnosis and treatment	*Difference in the cluster-level counts* 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.	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. Adjusting for cluster-level baseline covariates used to stratify randomization.
Secondary objectives		
Secondary objective 1: Compare two active TB case-finding interventions in terms of effectiveness in increasing uptake of TPT	*Difference in the cluster-level counts* of study region residents initiating TPT during intervention periods, comparing periods in which regions performed hotspot-focused ACF/TPT to those in	A negative binomial regression model with robust standard errors to account for clustering, and fixed effects for periods. Analysis will be stratified by time period: before/after April 24, 2024, when we limited

OBJECTIVES	Measures	Analytical approach
	which facility-based ACF/TPT was performed	TPT referral eligibility to contacts and people with HIV.
Secondary objective 2a: Estimate impact of active TB case-finding interventions on TB treatment initiations compared to no intervention. (Comparisons will be done for each intervention separately, and for the two interventions in aggregate.)	*Difference in the cluster-level count*s of study region residents notified as initiating treatment for bacteriologically confirmed new or relapsed pulmonary TB, comparing intervention regions to control regions.	A negative binomial regression model with robust standard errors to account for clustering, and fixed effects for periods.
	As above, comparing the intervention months versus no-intervention (washout) months in the same clusters.	A negative binomial regression model with robust standard errors to account for clustering, and a fixed effect for intervention vs washout over the study period
Secondary objective 2b: Estimate impact of active TB case-finding interventions on population TB burden, compared to no intervention.	Evaluate trends in the number of TB notifications over the intervention periods comparing intervention clusters to control clusters.	Graphical display of the TB notifications by arm (facility, hotspot, control) will be generated. A regression model (log-normal/Poisson link) will be used to quantify the nonlinear (arm x time) effects comparing intervention to control clusters utilizing all data points from the duration of the study. (Reference: Nonyane et al, BMJ Public Health. 2023 Sep 14;1(1):e000070.)
	Evaluate trends in the yield of the intervention over time, among screening participants.	Graphical display of screening yield by cluster and arm over time, within period and across periods. Regression to test for nonzero time trend across periods, adjusting for cluster and time.
Secondary objective 3: i*ntervention steps cascade* Compare the implementation of the two interventions: hotspot-focused and facility-based ACF/TPT -	• Total number of people screened for TB with each intervention • Proportion of enrolled participants diagnosed with TB based on Xpert positive sputum within the study's screening algorithm • Proportion of diagnosed participants confirmed to have initiated treatment for TB. (Note: The product of these three measures is the number of people diagnosed and treated through study participation – an endpoint listed above and in the original protocol.)	Display as bar graphs, with bars representing different study arms for each measure and where appropriate for proportions, add 95% confidence intervals. Generalized linear models with a logit link and random effects for clustering will be used to compare the odds between the two arms of enrolled participants (a) being diagnosed with TB and (b) starting TB treatment, adjusting for study period effects. Additional exploratory analyses will consider other TB diagnoses resulting from study activities, e.g. after clinical referral for abnormal X-ray, and will use linked treatment-register records to evaluate the treatment completion step of the cascade.
Secondary objective 4: Estimate costs and cost effectiveness of any	• Intervention costs: overall, per TB case detected, and per incremental treatment notification	• Ingredients-based costing from a modified societal perspective • Markov modeling of health outcomes to estimate DALYs averted using a

OBJECTIVES	Measures	Analytical approach
ACF/TPT intervention that is effective	• Incremental cost per DALY averted, comparing more vs less effective intervention and more effective intervention vs standard of care	modified societal perspective and lifetime time horizon • One-way, multi-way, and probabilistic sensitivity analyses
Tertiary/Exploratory		
Tertiary/Exploratory objective 1: Compare intervention effectiveness to a control of national trends	Compare time trend in rate of bacteriologically confirmed new or relapsed pulmonary TB notification, comparing intervention regions in aggregate to national notification rate	As for Secondary objective 2b. Will use 2024 population estimates throughout, in study regions and nationally
Tertiary/Exploratory objective 2: Understand how reach and effectiveness differ by sex, location, and clinical covariates	Key effectiveness and implementation outcomes (including 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	Summary statistics – counts or proportions as appropriate – of the outcomes, stratified by study arm and individual characteristics age (<15 [contacts only], 15-25, 25-40, >40), sex (male, female), HIV status (HIV negative/unknown, 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). GLMMs to evaluate associations between individual characteristics and the outcome of being diagnosed with TB, with an interaction with study arm.
Tertiary/Exploratory objective 3: One-year notification of TB among participants with presumptive-TB X-ray result and negative sputum	Proportion of participants with presumptive TB X-ray results and negative sputum who test positive for TB disease at 1 year since enrollment	Summary statistics – Proportion and corresponding Wilson score-based 95% confidence interval, (1) as self-reported among those who complete 2-week and/or 1-year follow-up phone calls, and (2) estimated from probabilistic matching of screening participants to treatment register data
Tertiary/Exploratory objective 4: Primary effectiveness outcome comparing rate per population size	Difference in the cluster-level rates per 100,000 of TB notifications, using 2024 census data as a denominator	T-test to compare test null hypothesis that rates are equal between the two arms, after a log-transformation if necessary. Negative binomial regression model with robust standard errors to account for clustering, and adjusting for the cluster-level baseline covariates used to stratify randomization.