Statistical Analysis Plan: HCD-CoP Study

NCT05640648

Trial Title	A User-Centered Strategy to Improve Delivery of TB Contact Investigation in Uganda: A Stepped-Wedge Cluster Randomized Implementation Trial
Grant Title	Human-centered Design and Communities of Practice to Improve Delivery of Home-based TB Contact Investigation in Uganda
Grant Acronym	HCD-CoP
Trial Registration	ClinicalTrials.org
Principal Investigators	J. Lucian (Luke) Davis, Achilles Katamba
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I. Introduction

1. Study Aims

Primary Objective

Aim 1: To compare the implementation, effectiveness, and public health impact of a user-centered strategy versus the standard strategy for implementation of TB contact investigation in a stepped-wedge, cluster-randomized implementation trial.

- ***User-centered Strategy:*** Training + Supportive Supervision + Electronic Data Collection + Facilitation Tools + Communities of Practice
- ***Standard Strategy*:** Training + Supportive Supervision + Electronic Data Collection

Secondary Objectives

Aim 2: To identify processes and contextual factors that influence the implementation, effectiveness, and public health impact of the user-centered contact investigation strategy.

Aim 3: To compare the costs and epidemiological impact of the user-centered and standard implementation strategies for TB contact investigation.

Overview

This statistical analysis plan covers the primary objectives of assessing the implementation and key secondary effectiveness and public health impact outcomes. **This document will not further address the trial's secondary objectives of assessing implementation fidelity and context (Aim 2) and implementation costs and impact at scale (Aim 3).** Study endpoints will be evaluated through a review of data entered into the HCD-CoP CommCare (Dimagi, Boston, MA) database by community health workers as part of their routine TB contact investigation activities, with validation of effectiveness endpoints using source data entered into Uganda National TB and Leprosy Programme TB treatment registers for all patients initiating TB treatment at participating health facilities. Trial results reporting will follow the CONSORT 2010 statement extension for stepped-wedge trials (**SWT**).[1, 2] This statistical analysis plan is written in support of and is entirely consistent with the full trial protocol; however, in case of any discrepancies, this statistical analysis plan takes precedence.

1. Trial Summary

Trial Design

The study proposes to conduct a stepped-wedge, cluster-randomized implementation trial of a novel, user-centered implementation strategy for the delivery of TB contact investigation at 12 TB diagnostic and treatment units (DTUs) located at health facilities in central Uganda. The trial over will proceed over the course of 16 trial steps, each 8 weeks in duration, with the intervention period lasting from as little as 16 weeks up to 56 weeks at the participating facilities. We will use a complete stepped-wedge design, including an 8-week transition period for training and initial adoption, followed by 8 to 52 weeks of post-intervention data collection at each site. Data collected during the transition periods will not be included in the final analysis. In addition, the trial will be paused for 6 weeks during the annual 2022-2023 year-end holiday period (12 December 2022 through 15 January 2023; all transition periods falling during and after this pause period will be delayed by six weeks and patients recruited during this period, as well as the data of their contacts, will be excluded from the trial.[§] The rationale for this pause is that staffing levels and patient visits are low during this period, and without exclusion, this could bias the trial results in uncertain ways.

[§]**Version 2.0 Update:** On 15 October 2022, the President of Uganda announced Ebola-related public health restrictions preventing public movement in two districts where two study sites are located: Mubende and Kasambya. As a result, the principal investigators immediately paused all new introductions of the study intervention effective immediately for the subsequent 8-week period ending 11 December 2022, effectively extending the previously proposed 6-week study pause by at least 14 weeks. The original schema is shown below in Figure 1, and an updated schema is shown below in Figure 2.

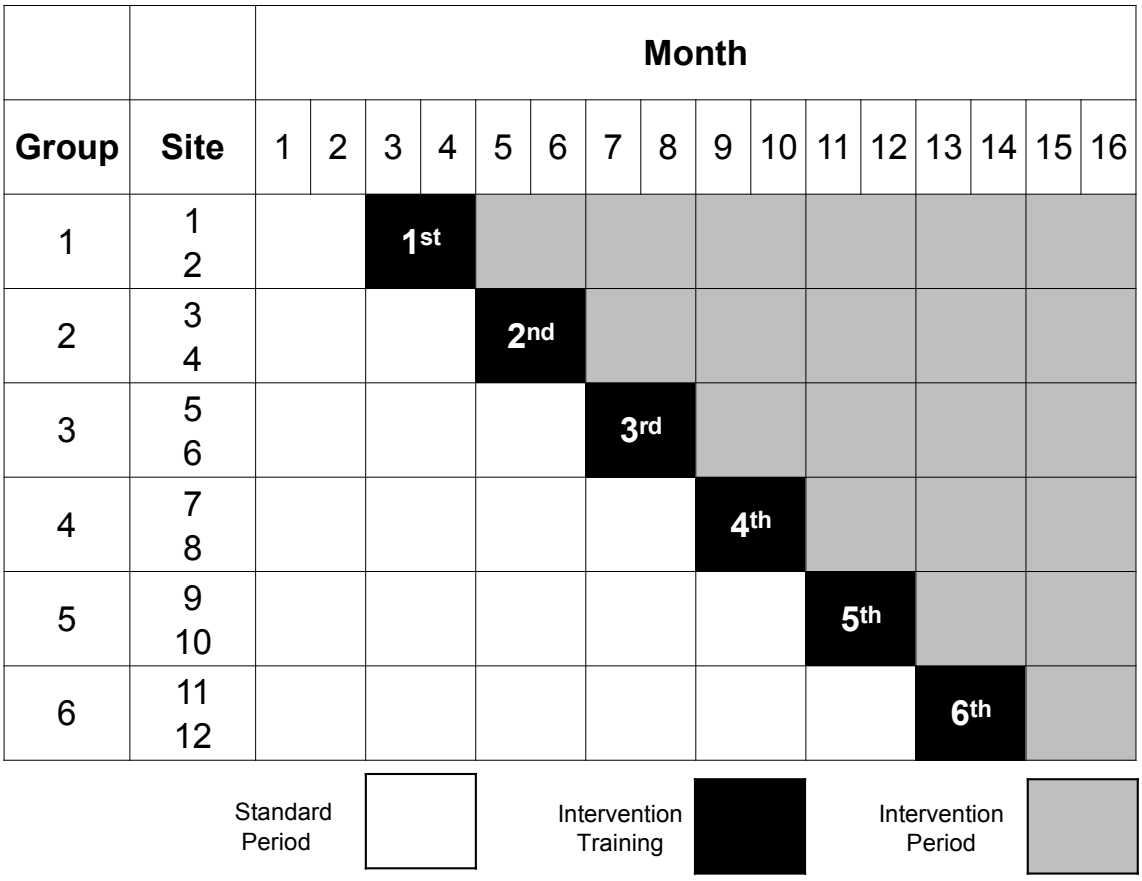

Figure 1. HCD-CoP Intervention Randomization and Enrolment Schedule.
Legend: Ordinal numbers indicate the cross-over sequence from standard to the intervention period. Note that pause periods are not shown in the current figure.

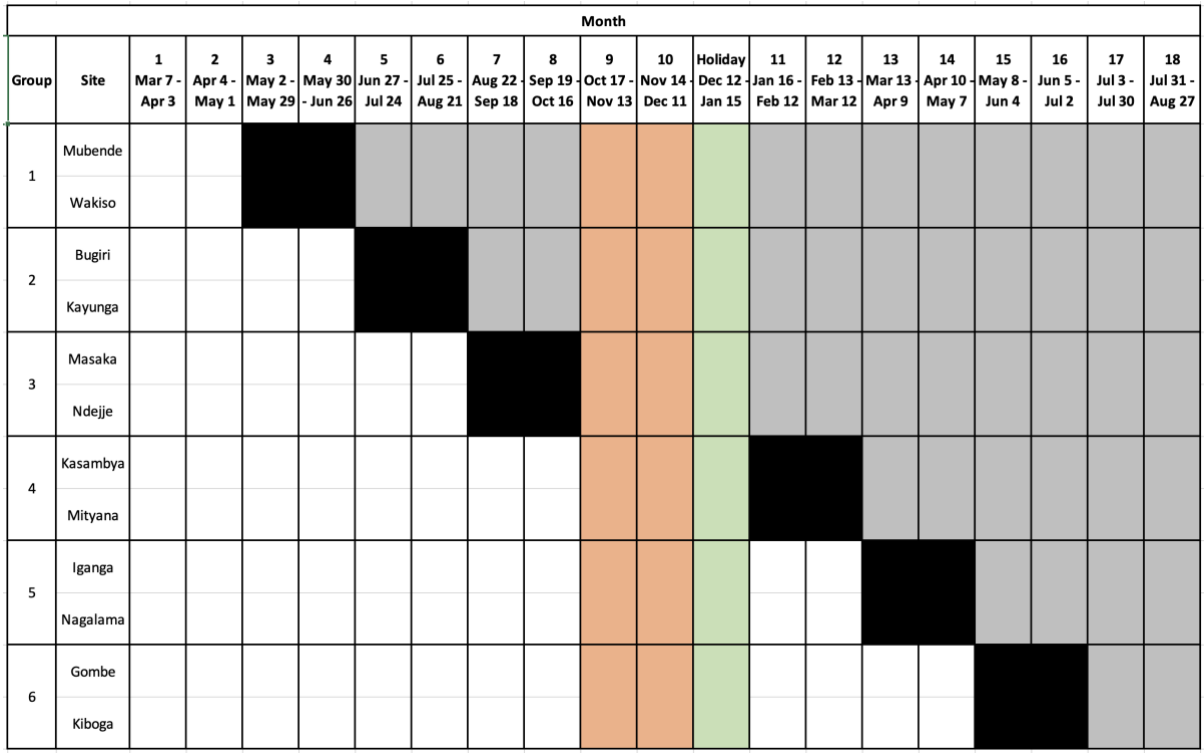

Figure 2. Modified study schema, with post-randomization site and cluster assignments, and enrollment pauses for Ebola Virus Disease lockdowns in October-December 2022, and low anticipated enrollments during the holiday period.

Study Population

Eligibility Criteria

A. *Site-level Inclusion Criteria*

- Diagnoses ≥12 index TB cases/month based on 2021 Uganda DHIS2 TB surveillance reports
- Located outside Kampala District (as defined by the Kampala Capital City Authority Boundary)
- Located ≤180 km from Kampala City

B. *Site-level Exclusion Criteria*

- Site leaders decline to participate in the study

C. *Patient-level Inclusion Criteria*

- Index Persons with TB
  - Adults and children recorded as new TB cases in the TB treatment register
  - Residing ≤40 km from the clinic
- Contact Persons
  - Adults and children reporting ≥12 cumulative hours with the index case inside an enclosed space during the previous 3 months
    - Those sleeping ≥1 day or night under the same roof may be called “household” contacts.
    - Others not meeting this criterion may be called non-household “close” contacts.

D. *Patient-level Exclusion Criteria*

- Index Persons with TB
  - Lacking the mental capacity to consent to contact investigation procedures
  - Lacking contacts, as defined above under patient-level inclusion criteria
  - Diagnosed or referred for evaluation as a DR-TB patient (whether possible or confirmed)
  - Previously completed TB contact investigation within the last two months
  - Declining to refer close contacts for contact investigation procedures
- Contact Persons
  - Lacking the mental capacity to consent to contact investigation procedures
  - Currently taking treatment for active TB
  - Declining contact investigation procedures

Target Setting and Enrolment Sites

Our target settings include urban and peri-urban communities surrounding clinics and hospitals with TB treatment units. Our target population consists of all household and non-household close contact persons of newly diagnosed persons with TB. We identified trial sites from a list of all TB Treatment Units in Central Uganda reporting 12 or more index TB cases diagnosed each month. Study staff reviewed the 2019 TB diagnosis and treatment data available in the Uganda District Health Information Services 2 (DHIS2) national surveillance database, focusing on those outside but within 180 km of the boundaries of the capital city of Kampala (where we previously implemented contact investigation at all public health facilities). We verified the number of index cases during on-site evaluations of clinical registers in 2021. We confirmed the counts of index cases and contacts during a 2-month run-in period at each site just prior to launching the trial.

Study staff obtained permission from District Health Officials and Health Center Directors to visit health centers to confirm site eligibility and assess interest in study participation. At the site assessment visit, study staff administered a site readiness survey that gathered information on the following aspects of readiness to inform implementation training: (1) human resources and procedures for carrying out TB contact investigation based on the Uganda National TB Contact Investigation guidelines; (2) general TB health systems readiness using elements derived from the Service Availability and Readiness Assessments (SARA) surveys; and (3) organizational readiness using domains and constructs from the Consolidated Framework for Implementation Research (**CFIR**).

Health centers that were confirmed to be eligible and expressed interest in participating in the study were reviewed with Uganda NTLP Director for approval. After selecting and approving the study sites, research staff met with District Health Officers (**DHO**) and Facility-Administrators-in-Charge to provide information about the project and request their participation as trial sites via a formal invitation letter from the Uganda TB Implementation Research Consortium.

Of note, we selected the final list of 12 sites in consultation with the trial statistician (to minimize the potential for site-level variation that could impact power).

Below we provide estimates of the expected proportions for enrolled participants during the standard and user-centered implementation periods based on our previous collection from similar clinics in Kampala and Mukono. These estimates include both a realistic endpoint and an optimistic endpoint. The sample size calculations are based on the realistic endpoint, but the optimistic endpoint is shared to show a potentially clinically meaningful outcome.

The estimates are based on full-year data from 2019, with assumptions laid out in the Supplement, Tables S1-S3. A review of the 2021 registers confirms similar site volumes as 2019.

Evidence-based Practice: TB Contact Investigation in Uganda

Participants in both the pre-intervention and intervention periods will undergo contact investigation following procedures aligned with the 2019 Uganda Ministry of Health Operational Guide, which defines the standard of care, evidence-based practice of TB contact investigation in Uganda. Briefly, facility-based community health workers will approach consecutive index TB patients newly diagnosed with TB and meeting eligibility criteria to invite them to participate in contact investigation. They may approach index patients in person in the clinic on the day of TB diagnosis or at any time up to and including the two-week follow-up visit in person or by telephone, using telephone contact information recorded in the TB treatment register to arrange or conduct the interview. After explaining the background and purpose of TB contact investigation to index patients, CHWs will ask for permission to make a community visit to screen contact persons for TB at a convenient time within 7 days after diagnosis or the first successful telephone contact, as per Uganda's guidelines. CHWs will continue to attempt to provide contact investigation until the two-month refill visit unless the index person with TB or the contacts explicitly decline. If the index person with TB does not wish to

participate in a community visit, he or she may bring his or her close contacts to the clinic for TB screening. It is recommended that CHWs conduct follow-up visits screening visits every six months for two years.

At the community visit, community health workers will be trained offer additional education and counseling aligned to contact tracing; perform symptom screening; provide a referral for HIV counseling and testing; collect and transport sputum to facilities for examination and testing; and communicate test results to participants. Following standard practice, individuals who complete TB evaluation (*i.e.,* screening, testing, and/or clinical evaluation as indicated) and are found to be negative for active TB may be referred for initiation of TB preventive therapy (**TPT**) whenever these services are locally available, which is increasingly the case following the issuance of national TPT guidelines in 2021.

Standard Implementation Strategy: Pre-Intervention Period

Training:

We will have a two-month pre-trial enrollment period to establish baseline site-level data characteristics. All CHWs and their supervisors will be simultaneously trained on standard TB contact investigation principles, data collection methods, and data quality assurance procedures two months prior to trial initiation. This will be preceded by on-site, supported enrollment training. To allow all sites to be fully trained in the first month, we split the 12 sites into two blocks such that two sites will simultaneously receive on-site, supported enrollment by one of our training teams. We will observe key site-level data characteristics for one month to establish the baseline data characteristics to inform sample size estimates and restricted randomization.

Supportive Supervision:

This will include oversight from the facility-based Uganda TB and Leprosy Programme supervisor in both the pre-intervention and intervention periods. The supervisor and the CHWs will receive data completeness reports that list their missing data collection forms. During the pre-intervention, CHWs will not receive any information on the outcomes of interest and will only receive reports on missing forms for data management and quality purposes.

Electronic Data Collection:

We customized a commercial survey application (CommCare, Dimagi, Boston, MA) designed for CHWs in resource-constrained settings. We trained all CHWs to accurately record all contact investigation data in electronic case-record forms using this application deployed on secure, trial-issued electronic tablets. The electronic data collection system includes decision support to prompt CHWs to deliver all contact investigation services. We also trained CHWs to accurately record data in the programmatic registers.

User-centered Implementation Strategy: Intervention Delivery Period

The intervention strategy seeks to optimize TB contact investigation through two sets of user-centered tools: 1) *The Implementation Facilitation Toolkit*, designed to address barriers to reaching cases and contacts through a set of participant-facing implementation components, and 2) *The Community of Practice Package*, designed to address barriers to adoption, implementation, and maintenance for community health workers through CHW-facing implementation components. These components are packaged under a unified program name and branding, entitled *Tuli Wamu Nawe*, an inspirational Luganda saying that translates as “We Are Together with You” and captures the strategy's user-centered philosophy. The strategy's overall goal is to improve implementation, effectiveness, and impact by better engaging cases/contacts and community health workers. We will implement the following intervention components, which were developed, pilot-tested, and refined following a human-centered design process.

- *Implementation Facilitation Package for TB Contact Investigation.*

    1. *TB 101 Booklet.* This eight-page graphical discussion guide in English and Luganda provides facts and critical information to address commonly asked questions, concerns, and misperceptions about

TB disease, transmission, treatment, and prevention. It also includes strategies for keeping healthy and holding back fear while facing the threat of TB. It is written in simple direct language and laid out in a short, colorful, and approachable format.

2. *Contact Identification Algorithm.* This is a structured screening tool to prompt index cases to recall all individuals with whom they have been in extended close contact during the prior three months, inside and outside the household. Community Health Workers will use the algorithm to record the names of all individuals who meet the criteria to be considered contacts. CHWs will then obtain permission from index patients to reach out to these individuals (or their parents/guardians) to offer TB screening, after agreeing upon the method of outreach.
3. *Sputum Collection Video.* This is a short instructional video, initial developed for use in Pakistan by InTuneForLife, a non-profit organisation of media professionals. After being culturally adapted for the Uganda setting, it is available in both Luganda and English, both in a 3.5 minute landscape format for tablets or a 2.5 minute portrait format for mobile phones. Community Health Workers or Riders play the video for symptomatic contacts to demonstrate the correct technique to be successful in sputum collection.
4. *Community Health Rider Program.* Carefully selected commercial motorcycle drivers will assist community health workers with household and community visit activities, including transporting CHWs, safely conducting sputum collection and transporting it to laboratories, and transporting contacts who need to visit the clinic for TB evaluation and/or treatment.
5. *HIV Testing Referral Card*. Contacts aged ≥15 who wish to undergo HIV testing will be provided a card to present at health facilities to receive expedited HIV counseling and testing.

- *Community of Practice Package for TB Contact Investigation.*

1. *Group Meetings.* These virtual meetings will host all community health workers from two paired sites, including site-level TB focal persons, workers, and riders. They will be held virtually, with staff joining from their sites weekly on Fridays. The leadership of the meetings will rotate through all CHWs and between sites and follow a structured format and duration. Staff will start by sharing recent experiences or questions, followed by a group activity (*e.g.*, review of the audit and feedback reports, structured didactics, meeting with the facility leaders, etc.) and close with establishing one or more improvement objectives for the next meeting.
2. *Audit and Feedback Reports.* Delivered monthly by email, these reports will display the contact investigation delivery cascade for the prior period as a running three-month average and facilitate comparisons of overall performance with the paired site.
3. *Group Chat Application.* CHWs and the site-level TB focal person will be linked to a shared Chat Group (*e.g.,* WhatsApp or a similar platform) where requests for advice or assistance or messages of encouragement and social support may be posted for response in real-time or asynchronous discussion. This forum may be facilitated by the TB focal person or the internally designated weekly leader of the CoP.

- Training.

  Training for the intervention period will be delivered in a manner that facilitates the stepped-wedge trial, as demonstrated in Fig 1. Trainers will train CHWs and CHRs from the two sites randomly assigned to each block on the proposed intervention strategy at the time when they are expected to cross over from the pre-intervention to the transition to the intervention period. The training will be structured as follows. We will conduct a debriefing session to resolve any spillover implementation challenges. After this 20-day training on the concepts and hands-on aspects of the intervention strategy, we will be confident that the CHWs will be able to independently enroll new TB patients and their contacts, troubleshoot, and resolve process-navigation-related issues (Table 1.)

Table 1. User-centred Strategy Training Layout	
Training activity detail	**Days**
Classroom Training(Concepts)	1-3
On-site Trainer-CHW co-enrollment	4-10
CHW independent enrollment training	11-20
Post enrollment training debriefing session	21-22

Definitions of process measures

Our data collection system will allow us to record and aggregate the numbers of patients passing through each step of the TB evaluation process into a delivery cascade that can be further stratified by important clinical and demographic characteristics. Constructing this cascade requires specification of relevant categories of participants eligible for different evaluation steps. Once eligibility is defined, dividing the number of individuals completing a step into the number eligible for that step will produce a ratio that may be termed the "*stepwise yield*" of contact investigation at that step. Finally, the *cumulative yield* may be measured as the number completing a cascade of processes divided by the number entering that cascade.

Contact investigation cascade process measures for index cases (the variable names used in the CommCare database specified in parentheses below).

1. **Invited:** Cases offered TB contact investigation (idxcons)
2. **Accepted:** Cases agreeing to TB contact investigation (idxcons), as defined by index patient interview date (idxrecruitdate)
3. **Encountered contacts:** Encountering ≥1 contact per index patient for TB contact investigation (ctinterviewdate),
4. **Reached contacts:** ≥1 contact successfully screened for TB symptoms, as defined by contact interview date (ctinterviewdate in conjunction with tbsymptoms)
    a) *Reached household contacts:* Cases with ≥1 household contact interviewed
    b) *Reached other close contacts:* Cases with ≥1 non-household contact interviewed

TB evaluation and treatment cascade process measures for TB contacts:

1. **Contacts Encountered:** Contact encountered by Community Health Worker (cascade may be stratified by household contact or non-household close contact status) (ctcons)
2. **Screened TB Symptom Positive:** Contacts reporting ≥1 of the following (tbsymptoms):
    a. Cough of any duration (ctcough), with or without sputum production
    b. Fever (including subjective fever) or chills (ctfever)
    c. Night sweats (ctnightsweats)
    d. Weight loss (estimated to be) ≥3 kg (ctweightloss), or poor weight gain among children aged <5 years (both subjective) (ctchildpoorweightgain)
    e. Child <5 who is tired or less playful (subjective) (ctchildtired)
    f. Child <5 who has noisy breathing or wheezing (ctchildwheezing)

Contacts who are "Screened TB Symptom Positive" are also considered "possible TB patients."

3. **Sputum collected and delivered:**
    a. *Sputum collected:* Sample logged as collected by a CHW (ctsputcommunitycollect)
    b. *Sputum received:* Sample logged as arrived in the laboratory (ctsputreceived)
4. **TB Evaluation Completed:** Contacts meeting ≥1 of the following criteria:

a. *TB Testing Completed:* Meeting ≥1 of the following criteria, as defined by analysis result/date recorded by CHW (ctsputanalysisdate):
   i. *Completed sputum smear microscopy exam (≥1 sample examined) (ctsmearrslt)*
   ii. *Completed GeneXpert (Xpert) testing (≥1 sample examined) (ctxpertrslt)*

b. *Completed TB Clinical Evaluation:* Evaluated by a clinician, as documented by a community health worker at one of the study sites (ctevaldate, cttbdiagnosedclinic)
   i. We will also include a sensitivity analysis incorporating self-report of TB evaluation completion at another site

c. *Completed Chest Radiography* (cttbexclusionclinic OR cttbdxbasisclinic):
   i. *Underwent chest radiography*
   ii. *Interpretation documented by a community health worker (i.e., consistent with active TB or not consistent with active TB)*

5. **TB Diagnosed:** Contacts meeting ≥1 of the following criteria:

   a. *Sputum AFB-smear positive* by standard grading criteria (regardless of staining technique or light modality), as recorded in any one of the following sources: TB Lab Register or TB Treatment Register (ctsmearrslt)

   b. *GeneXpert-positive* by standard grading criteria (any single sample higher than Trace, or two or more samples with Trace results), or as recorded in the TB Lab Register, TB Treatment Register, or on the TB Patient Treatment Card (ctxpertrslt)

   c. *Clinically diagnosed* with pulmonary or extrapulmonary TB without a microbiologic result (including those diagnosed based on chest radiography alone), as recorded in the TB Treatment Register or on the TB Patient Treatment Card (cttbdiagnosedclinic)

6. **TB Treated:** Recorded as initiating TB treatment in the TB Treatment Register or on the TB Patient Card (cttbrx AND cttbrxstartdate)

7. **TB Treatment Completed:** Completed 6-month visit within 8 months of treatment initiation, as documented in the TB Treatment Register or on the TB Patient Card, using WHO 2013 treatment outcome definitions.

8. **Eligible for TB Preventive Therapy:** Contacts who are

   a. Not diagnosed with TB, AND

   b. Meeting one of the following criteria

      i. *Child under 5 years (ctage), or*

      ii. *Person living with HIV (cthiv0 OR cthivclinic)*

      iii. *Older adolescent (age ≥15 years (ctage) and adult household and other close contacts with a positive tuberculin skin test (TST) (cttst) and in whom active TB has been excluded by symptoms and/or testing*

9. **TB Preventive Therapy Initiated:** Recorded as initiating TPT in the clinic TPT Register (ctipt AND ctiptstartdate)

Outcomes
Primary Outcome

a. **Implementation** (*i.e.,* implementation effectiveness)
   i. *Proportion of contacts who complete TB evaluation within 60 days of index patient treatment initiation (idxrxstartdate)*

a) *Outcome definition*: Number of contacts who complete TB evaluation within 60 days (ctevalcomplete60) of index patient treatment initiation divided by the total number of contacts screening TB symptom positive (ctevaleligible). This will be an aggregate, cluster-level, exposure-specific (control versus intervention) measurement.

b) *Outcome analysis*: Difference in log odds of the outcome between the intervention and control exposure periods using the Logit model (*n.b.*, this will be the same for all proportional outcomes)

Secondary Outcomes

a. **Effectiveness** (*i.e.*, clinical effectiveness)

i. *Proportion of contacts diagnosed with active TB (also known as the active TB treatment yield of TB contact investigation, or the number needed to screen):*

a) *Outcome definition:* Number of contacts diagnosed with active TB (definitions below) and initiated on treatment within 60 days of index patient treatment initiation divided by the total number of contacts encountered.

(i) Microbiologically confirmed active TB: Diagnosed by a positive AFB-smear microscopy result, GeneXpert result, or other accepted *Mtb*-specific microbiologic test *(e.g.,* urinary LAM or mycobacterial culture)

(ii) Clinically confirmed active TB: Active TB diagnosed clinically, based on clinically diagnosed extra-pulmonary TB or a decision to initiate presumptively for active pulmonary TB.

b) *Outcome analysis:* As above

ii. *Proportion of contacts initiating TB preventative therapy (TB preventative therapy yield of TB contact investigation):*

a) *Outcome definition:* Number of TB contacts initiated on TB preventive therapy within 60 days of index patient treatment initiation divided by the total number of contacts eligible for TB preventive therapy

(i) Children under age 5

(ii) Persons living with HIV

(iii) Older adolescent (age ≥15 years and adult household and other close contacts with a positive TST and in whom active TB has been excluded by symptoms and/or testing

b) *Outcome analysis:* As above

b. **Public Health Impact** (*i.e.*, public health effectiveness)

i. *Count of contacts diagnosed with active TB:*

a) *Outcome definition:* Number of contacts diagnosed with active TB (definitions below) and initiated on treatment within 60 days of index patient treatment initiation

(i) Microbiologically confirmed, as defined above

(ii) Clinically confirmed, as defined above

c) *Outcome analysis:* Difference in the natural log of the counts of the outcome between the intervention and control exposure periods using the Poisson model (*n.b.*, this will be the same for all count outcomes)

ii. *Count of contacts initiating TB preventative therapy (TB preventative therapy yield of TB contact investigation):*

a) *Outcome definition:* Number of contacts initiated on TB preventative therapy within 60 days of index patient treatment initiation

b) *Outcome analysis:* As above

iii. *Proportion of all TB cases among contacts:*

a) *Outcome definition:* Number of newly diagnosed TB cases who are contacts among all those TB cases, divided by the total number index TB patients

b) *Outcome analysis:* As above

Additional Outcomes

a. **Efficiency** (*i.e.*, the stepwise yield of contact investigation)

i. Proportion completing each step of the contact tracing cascade (for cases a(i) through a(vi) and for contacts b(i) through b(vii)), with the denominator the number eligible at the end of the previous step.

a) Proportion of index cases

(i) who were invited to contact investigation (count of all index patients in treatment registers),

(ii) who accepted the invitation (idxcons), and

(iii) who had at least one contact interviewed (_merge)

b) Proportion of reported contacts

(i) who were screened for TB symptoms (ctcons),

(ii) who were found to have TB symptoms (tbsymptoms),

(iii) who were evaluated for active TB based (ctevalcomplete),

1. who were diagnosed with active TB (tbpositive),

a. who initiated TB treatment (within 2 months) (cttbrx combined with cttbrxstartdate),

(iv) who were found not to have active TB (as a proportion of those who had no symptoms (ctcons-tbsymptoms) plus those who had symptoms but were found not to have active TB (ctevalcomplete-tbpositive))

1. who initiated TB preventative therapy (within 2 months) (ctipt combined with ctiptstartdate)

b. **Timeliness** (*i.e.*, time to effective implementation)

i. *Time to recruitment to contact investigation*

a) *Outcome definition:* Days from index patient treatment initiation (idxrxstartdate) to case acceptance of contact investigation invitation among eligible cases (idxrecruitdate)

b) *Outcome analysis*: Difference in time-to-event between the intervention and control exposure periods using Survival analysis, *n.b.*, this will be the same for all time-to-event outcomes)

ii. *Time to contact screening visit*

a) *Outcome definition:* Days from index patient treatment initiation (idxrxstartdate) to contact TB screening (ctinterviewdate)

b) *Outcome analysis:* As above

iii. *Time to completion of contact evaluation*

a) *Outcome definition:* Days from index patient treatment initiation (idxrxstartdate) to completion of contact evaluation, defined as completion of sputum testing (ctsputanalysisdate), or, if sputum testing not completed, completion of clinical evaluation or chest radiography (ctevaldate), whichever comes first.

b) *Outcome analysis:* As above

c. **Equity** (*i.e.*, pre-specified, stratified analyses for all primary and secondary outcomes)

i. *Clinic site/community subgroups*

a) *Outcome definition:* Days from index patient treatment initiation to completion of contact evaluation, defined as completion of sputum testing, or, if sputum testing is not completed, completion of clinical evaluation or chest radiography, whichever comes first.

b) *Outcome analysis:* As for the underlying outcome above, including both restricted and within-group analyses

ii. *Individual patient subgroups*

a) *Outcome definition:* Strata defined below

(i) Age (ctage)

1. Adults (age ≥18)
2. Adolescents (age 10-17)
3. Older Children (age 5-9)
4. Young Children (under age 5)

(ii) HIV status, at baseline (cthiv0) or clinic follow-up (cthivclinic)

1. Persons living with HIV
2. Persons not living with HIV
3. Unknown HIV status

(iii) Contact type

1. Household contact
2. Non-household close contact

b) *Outcome analysis:* As above

Power and sample size calculation

Power and sample size calculations for the proposed stepped-wedge, cluster-randomized trial assume two levels of clustering. Representing the first level of clustering (rho-alpha) at intraclass correlation coefficient (ICC) level 1 are index TB patients nested within clinics and representing the second level of clustering (rho-beta) at ICC level 2 are contacts nested within index TB patients. According to pre-trial empirical data collected at 12 clinics between 1st January 2022 and 6th March 2022, there were 781 total contacts of 273 index TB patients, giving an average of 22.7 index TB patients in each of the 12 clinics, and 2.86 contacts per index TB case during a 2-month block period.

To inform our sample size calculations, we used a conservative estimate of the average number of index TB patients of 11 per clinic per 8-week block period (g), assuming a rho-alpha of 0.172 and rho-beta of 0.647 from our preliminary data, and an average number of symptomatic contacts per index TB case (m) of 1, as well as a pre-intervention proportion of patients completing treatment (p1) of 0.4, a post-intervention proportion of treatment completion (p2) of 0.6, the number of clusters crossing at each step (k) of 2, and total steps (steps) of 6.

Using the Stata command:
steppedwedgeTwoLevelsD, binomial complete(1) vartotal(1) p1(0.4) p2(0.6) m(1) k(2) rho(0.172) rho2(0.647) alpha(0.05) steps(6) g(11),

We estimate that the trial will conservatively need 924 total symptomatic contacts of index TB patients to achieve a power of **99**%. Sample size estimates were reached using PASS 15 and Stata 16, with an extension to account for multiple levels of clustering as per Hemming et al.[3] and Davis-Plourde [4]. Although some sample size estimators predict 100% power, 100% power is not theoretically achievable, and therefore rendered as 99%. Because index patients and contacts are participants in routine services, we will not limit enrollment if it exceeds these numbers, which we project may be higher by four-fold or greater if the intervention strategy is highly effective.

Tests for Two Proportions in a Stepped-Wedge Cluster-Randomized Design

Design type: Complete
Test statistic: Wald Z-Test
H_0: P1 - P2 = 0.
H_A: P1 - P2 = D1 ≠ 0.

ICC (intra-cluster correlation coefficient (rho)) measures the correlation of observations within a group/cluster. It indicates the dependency of observations on the group/cluster they belong to. Mathematically, it is calculated as the variance between groups/clusters divided by the total variance (which is variance between groups plus variance within groups). Thus, the higher the correlation within the groups (meaning less variability within groups/clusters), the lower the variance within groups leading to a higher ICC. The converse is also true, in that the lower the correlation within groups (meaning less variability within groups/clusters), the higher the variance within groups leading to a lower ICC.

Table 2: Power and sample size (total number of symptomatic contacts of index TB patients) estimation

Clusters S/T/k/K	Sample size m/g	Control (P1)	Intvnt (P2)	(D1)	Rho alpha (rho)	Rho beta (rho2)	Alpha	Symptomatic contacts (N)	Design power
6/7/2/12	**1/11**	**0.20**	**0.40**	**0.20**	**0.172**	**0.647**	**0.05**	**924**	**1.0000**
6/7/2/12	1/11	0.20	0.45	0.25	0.172	0.647	0.05	924	1.0000
6/7/2/12	1/11	0.25	0.45	0.20	0.172	0.647	0.05	924	1.0000
6/7/2/12	1/11	0.25	0.50	0.25	0.172	0.647	0.05	924	1.0000
5/6/2/10	1/11	0.20	0.40	0.20	0.172	0.647	0.05	660	1.0000
5/6/2/10	1/11	0.20	0.45	0.25	0.172	0.647	0.05	660	1.0000
5/6/2/10	1/11	0.25	0.45	0.20	0.172	0.647	0.05	660	0.9999
5/6/2/10	1/11	0.25	0.50	0.25	0.172	0.647	0.05	660	1.0000
4/5/2/8	**1/11**	**0.20**	**0.40**	**0.20**	**0.172**	**0.647**	**0.05**	**440**	**0.9983**
4/5/2/8	1/11	0.20	0.45	0.25	0.172	0.647	0.05	440	1.0000
4/5/2/8	1/11	0.25	0.45	0.20	0.172	0.647	0.05	440	0.9948
4/5/2/8	1/11	0.25	0.50	0.25	0.172	0.647	0.05	440	0.9999

Definitions
S is the number of steps in the study design. S = T - 1.
T is the number of time periods in the study, including the baseline. T = S + 1
k is the number of clusters switching from control to treatment at each step.
K is the total number of clusters to be randomized.
m is the average number of contacts per index TB patient per 2-month block period.
g is the average number of index TB patients per 2-months block period

N is the total sample size of contacts from all index TB patients, clusters and time periods combined. N = m*g*T*K.
P1 is the control/baseline proportion.
P2 is the treatment proportion, assuming the alternative hypothesis.
D1 = P2 - P1 is the difference assuming the alternative hypothesis (H_A).
Rho-alpha (rho) is the ICC level 1 for index TB patients nested in clinics
Rho-beta (rho2) is the ICC level 2 for contacts nested in index TB patients
Alpha is the probability of rejecting the null hypothesis when it is true.

Summary
If we power for a minimum detectable difference of 0.20, a sample of 12 clinics/clusters in a complete stepped-wedge cluster-randomized design with 7 time periods (including the baseline), 6 steps, 2 clusters switching from pre-intervention (control) to post-intervention (treatment) at each step, two levels of ICC (rho-alpha of 0.172 and rho-beta of 0.647 from our pre-trial data), an average of 11 index TB patients per cluster per 2-months' time period, a minimum of 1 symptomatic contact per index TB patient, a total number of index TB patients needed for the trial is 924 which achieves 99% power for a minimum detectable proportion difference of 0.1 between a pre-intervention proportion of 0.2 and a post-intervention proportion of 0.4.
These and other sample size estimates are indicated under Scenario 1 in Table 2, in the upper panel in bold, black font.

We also are proposing sample size calculations for other contingencies. Specifically, we wish to plan for scenarios in which one or both sites in a paired-site cluster do not achieve the expected number of symptomatic contacts patients due to secular events, the whole pair will be excluded from the final analysis. Given the effect of a small number of clusters on the power of SWTs, we see two plausible scenarios namely:

i. *Scenario 2*: One pair of clusters is excluded from the final analysis. In this case, the number of steps reduces to 5, the time periods reduce to 6 and the number of clusters reduces to 10. The power estimates for this scenario are presented in Table 2 above, in the middle panel in blue ink.

ii. *Scenario 3*: Two pairs of clusters are excluded from the final analysis. In this case, the number of steps reduces to 4, the time periods reduce to 5 and the number of clusters reduces to 8. The power estimates for this scenario are presented in Table 2 above, in the lower panel in purple ink. This is the worst-case scenario. The estimates indicate that this scenario would have 99.8% for a minimum detectable proportion difference of 0.2 between a pre-intervention proportion of 0.2 and a post-intervention proportion of 0.4.

Blinding

The trial exposures will be open-label for participants and researchers, as blinding is not feasible given the complex and behaviorally focused nature of the intervention. The investigators and study staff will be masked to any presentations of aggregated data, except in the unlikely instance of an adverse event, or an under-enrollment problem identified by the trial data analysis team. *The trial data analysis team will have access to the aggregate data, which will include bi-monthly review of numbers of enrolled participants aggregated across all sites to prevent comparisons of standard and user-centered strategy implementation clusters*. Finally, two members of the trial data analysis team will be responsible for preparing audit and feedback reports for intervention periods. All CHWs will be notified of missing case report forms during both the control and intervention periods. During the intervention periods, CHWs will also receive performance reports, including identifying areas for improvement.

Randomization

Sequence generation for stepped wedge trials refers to the order in which clusters cross over from control to intervention. Following a baseline two-month period of data collection, the intervention strategy will be

introduced at two new sites every 2 months until all 12 sites (6 pairs) have transitioned from the standard to the user-centered implementation strategy (Figure 1).

In this trial, eligible health facilities (N=12) will be randomly assigned to one of the six sequences using a simple, restricted two-stage process. The two stages of randomization will be as follows. *First*, health facilities will be assigned into two strata (high- and low-volume) based on pre-randomization data indicating the number of newly diagnosed TB cases per month, as a surrogate for the primary outcome. The assumption is that within each stratum, there is an average number of symptomatic contacts per index TB patient. Therefore, the number of newly diagnosed TB cases per month reflects the density of contacts and this needs to be balanced for health facilities grouped/paired together in one cluster to ensure baseline homogeneity within each cluster and identical effect of a future secular trend. Specifically, each cluster will include one randomly selected low-volume and one randomly selected high-volume clinic. *Second*, clusters will be randomly assigned into the sequence order in which they will switch to the intervention.

This sequence of allocation restricted by sites will be determined through a two-stage random drawing during a public randomization ceremony held in Kampala, Uganda. A senior clinician representative of each health center (*e.g.,* the TB focal person), the Health Facility Administrator-in-Charge, and the District Health Officer will be invited to attend a public randomization ceremony chaired by the Uganda NTLP Director. In the first, so-called “Cluster Stage”, health facilities will be divided into high-volume and low-volume strata for cluster assignments. Each health center representative will draw, without replacement, one ball labeled with the cluster designation, until all sites are assigned in paired clusters. In the second and final, or “Group Stage,” the two representatives of each cluster will assign one representative to draw, without replacement, 1 of 6 balls (labeled 1, 2, 3, 4, 5, 6) from an opaque bag to choose the group. Group 1 will be the first group to cross over, Group 2 the second to cross over, and so on. The sites will follow this cross-over sequence at equally spaced, 2-month intervals during the trial period, starting at the beginning of month 3.

Statistical Methods

For standardization purposes, the start of effective intervention exposure for clusters will be considered the first Monday of the next calendar week after the end of each 8-week transition period. This standardization will help fix the trial period slices and improve statistical efficiency for the within-period analyses. We will use a cluster-period mixed-effects logit model[5, 6] to assess differences between post-intervention and pre-intervention periods with regard to the proportion of contacts who completed TB evaluation within 60 days of index treatment initiation, the proportion of contacts diagnosed with active TB, the proportion of contacts initiating TB preventative therapy and proportion of all TB cases among contacts. We will use a cluster-period mixed-effects Poisson model[5, 6] to assess the difference between post-intervention and pre-intervention periods with regard to the count of contacts diagnosed with active TB and the count of contacts initiated on TB preventative therapy within and between periods. We will test for secular trends using both fixed and random effects. If secular trends are present, we will use a segmented regression model.

a. Dataset assembly, cleaning, and creation of new variables

Merged datasets will be extracted from CommCare, transferred to Stata, and re-arranged into working analytic files and checked for completeness. We will generate time-slice and exposure variables including the control-intervention exposure defining variable (var), the cluster-month *var*, cluster-exposure *var*, exposure-month *var,* and the exposure-time-cluster variable. The transition period will be excluded from the analysis as indicated in the trial design section 2.1 above.

There are 12 study sites that were assigned into six groups (2 facilities per group) and one group at a time will be switched from the standard pre-intervention to the user-centered implementation strategy during 8-week training and transition intervals in a randomly assigned order. Within each of the 6 groups, cluster-level covariates (outcomes, predictors, and confounders) will be formed by aggregating individual-level participants' data. For every cluster, each outcome (primary, secondary, and implementation) occurring

during the study period will be assigned to that cluster, the exposure condition (pre-intervention or intervention), and the trial month in which it occurred. A group-specific summary measure of the outcome, Y_{ij} (for *i* exposure and *j* period) will be calculated as a mean (SD) for continuous and count variables, and mean proportion for binary variables. From the Y_{ij}s, we will then calculate the cluster-period summaries ΣY_{ij} /n, where n=number of months in *i* exposure, and estimate unadjusted period-specific intervention effect (θ) based on these cluster-period summaries.

b. Baseline assessment and trend analysis

Baseline measures of all outcomes will be calculated using data collected in the pre-intervention period months 1 and 2 (Figure 1).

Within-period analyses comprise period-specific assessments where aggregated outcomes of groups in the pre-intervention exposure are compared with those of groups receiving the intervention exposure during the same trial month(s). For between-period analyses, outcomes for each group are compared to those of the same group in the intervention versus pre-intervention exposures, *i.e.*, cluster-specific, control-intervention comparisons across different time periods. Post-baseline measures will include pre-intervention and intervention exposure since groups will enter intervention exposure at varying times. For clusters still in the control exposure period, each subsequent trial month after study month 2 before the commencement of their transition period will be analyzed as the pre-intervention, post-baseline period. The start of effective intervention exposure (*i.e.,* the post-transition period) for each group will be the first day of the calendar month following the 2nd month of the transition interval.

c. Intervention Effect Analysis

The effect of the intervention will be assessed for implementation effectiveness, clinical effectiveness, public health effectiveness, and timeliness. Other analyses include equity, as determined by stratified analyses specific to sub-groups of interest. The primary trial analysis is implementation effectiveness; other analyses are secondary. The intervention effect will be measured as the ratio of outcomes in the intervention period (numerator) to those in the pre-intervention/control period (denominator), adjusting for potential confounders and clustering. The data in this trial are hierarchical and clustered. As a practical matter, data are clustered at 2 levels; first, the household (index patient) cluster, including any contacts of index patients and likely from multiple households around the index patient; and second, at the clinic level - multiple CHWs are working towards care. The clinic-level variance will be adjusted for as a random effect. It might lead to similar levels of completion. Analyses will adjust for clustering at those levels with outcomes will be aggregated at the clinic level to give more stable proportions. As indicated in sections 2.9 to 2.11, iib, proportion outcomes will be assessed as the difference in log odds of the outcome between the intervention and control exposure periods using the mixed-effects logit model. When the proportion with the outcome is >15%, odds ratios yield biased estimates; in these cases, we will determine the intervention effect by comparing prevalence risk ratios (PRRs) / proportion ratios (PRs) rather than ORs. To achieve this, we will use a modified mixed-effects Poisson generalized linear model (Stata command: meglm) with family(poisson) link(log), which estimates prevalence risk ratios (PRRs)/proportion ratios (PRs) and mitigates the overestimation effect of ORs when the proportion with the outcome is greater than 15%. These models will be used for the proportion of outcomes (implementation effectiveness and clinical effectiveness). Mixed effects Poisson models (mepoisson) will be used for count outcomes (public health effectiveness). For time-to-event outcomes, mixed effects parametric survival analysis models (mestreg) will be used.

The random intercept and random slope models take the general form of

$Y_{ijk} = \mu + \beta_j + \theta X_{ij} + u_i + e_{ijk}$, ... Equation 1

where y_{ijk} is the outcome of individual *k* in period *j* from clinic *i*, μ is the mean outcome in the first period, β_j is the difference between period j and the first period with $\beta_1=0$, θ is the intervention effect, X_{ij} is 1 if cluster i received the intervention in period j and 0 otherwise, u_i is a random effect for cluster, and e_{ijk} is the within-cluster variability.

In a stepped wedge trial, the outcomes will be aggregated at cluster level hence the general model form will be

$Y_t = \mu + \beta_j + \theta X_{ij} + u_i + e_{ijk}$, …….. Equation 2

where Y_t = aggregated outcome within each time slice t, calculated from Y_{ijk} (for *i* exposure, *j* period (month) and cluster *k*). We will adjust for unbalanced time-independent variables at baseline and confounders. The proportion of the outcome variable will be calculated for each site and cluster for each study time-exposure slice.

For between-period (horizontal) comparisons, comparative analysis is done at cluster level hence the general model form is:

$\text{logit}(Y_{jt}) = \alpha + \beta x_{jt} + \Sigma \gamma_t z_t + u_j$ …….. Equation 3

where *j* indexes the clusters, *t* indexes the steps, x_{jt} indicates a cluster and exposure; is coded 0 when the *j*th cluster is in pre-intervention (control) exposure and 1 when it is in the post-intervention (intervention); *β* represents the intervention effect, γ_t represents the time-specific effects, z_t the steps and u_j represents the cluster-level random effects (within-cluster correlation).

Within-period (vertical) comparisons are done by fitting a model as in Equation 4
$\text{logit}(Y_{jt}) = \alpha + \beta x_{jt} + \Sigma \gamma_t z_t + u_j$ …….. Equation 4

- where x_{jt} indicates a cluster and time and is coded 0 for clusters in pre-intervention (control) exposure and 1 for clusters in the post-intervention (intervention); *β* represents the intervention effect, and γ_t represents the time vertical slices.

Alternative Statistical analyses[§]

[§]**Version 2.0 Update:** It was noted above that on 15 October 2022, the President of Uganda announced Ebola-related public health restrictions preventing public movement in two districts where two study sites are located: Mubende and Kasambya. As a result, the principal investigators immediately paused all new introductions of the study intervention according to the schedule noted above. The effects and the duration of this public health emergency are currently unknown, but they may adversely affect both the implementation of this trial and its outcomes. The alternate analysis plans below may become especially relevant if this outbreak invalidates previous assumptions about participant and/or outcome accrual and feasible analytical approaches.

We face a high-level of uncertainty about how the Ebola outbreak and/or other secular trends will affect participant and/or outcome accrual or prior assumptions about sample size and feasible analytical approaches. Accordingly, we lay out our proposed approach below, based on currently available information and our desire to pre-specify the analysis, while recognizing that there may be need to alter these plans if we encounter problems with the analysis, with appropriate justification. The flexibility of our analysis options highlights a strength of the trial design: that is, its pragmatism in the face of an extreme event.

Individual level data will be collapsed at health facility and cluster levels by trial month in both control and intervention exposure periods to create panel data. We will estimate the difference in primary outcome by comparing control and intervention periods using aggregated data. Two models will be considered namely 1) ***Random effects logit model (xtlogit)*** for binary dependent outcome where the probability of the outcome is determined by the cumulative logit distribution function and accommodates various correlation structures; and 2) **Random effects GEE model (xtreg, re)**; this model accommodates fewer correlation structures than

the former. Both models allow cluster-level aggregated data to vary across time by cluster. The multivariable model will include cluster-level covariates. We will test various correlation structures and choose the final model using likelihood ratio tests and information criteria (AIC, BIC and QIC).

3.1.2 Populations and subgroups to be analyzed

a. *Populations*

- Intention-to-treat (ITT): The primary analysis will consider the intention-to-treat population, including all index patients eligible at all sites and their identified and screened contacts. Pre-intervention patients in the intention-to-treat population will be those who were diagnosed at a site during the pre-intervention period, and subsequently, their contacts will be considered pre-intervention contacts. Intervention period patients in the ITT population will be those who were diagnosed with TB at a site during the intervention period, and subsequently, their contacts will be considered intervention contacts.

- A per-protocol analysis is not relevant in this case since all community health workers at the site during the intervention period will be exposed to the user-centered implementation strategy, and it is not possible to quantitatively measure adherence to the implementation components in the context of the pragmatic features of the trial.

b. *Adjusted analyses:* In the presence of secular trends (and thus analysis at the individual level), the adjusted analyses will consider age (continuous), sex, HIV status, and any other baseline characteristics found to be imbalanced between control and intervention periods. In the absence of secular trends (and thus aggregated analysis by site and by month), the adjusted analyses will consider covariates such as the proportion of male vs. female, mean age, health center level, health center location (peri-urban vs. rural), and GDP of health center district (low vs. high). Data will be collapsed by the sum of total outcomes for binary outcome variables and mean value for any continuous variables (*e.g.*, age). We will adjust for trial period as appropriate for stepped wedge trial data analysis.

c. *Subgroup analyses*: In the case of individual patient data analysis, five subgroups will be analyzed using the ITT population.

- Age

- Sex: All eligible patients at randomized health centers will be divided into two groups by sex and analyzed separately.

- HIV Status: All eligible patients at randomized health centers will be divided into two groups by HIV status (living with HIV and HIV-negative/unknown) and analyzed separately. If ≤5% of the population is missing HIV status, we will analyze the outcome first without accounting for the missing data. If >5% are missing data, we will use multivariate multiple imputation to account for missing HIV status.

- Site: Eligible patients at each of the 12 health centers will be analyzed separately.

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