Trials

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Evaluation of a combined tuberculosis case-finding, treatment and prevention strategy in Thailand: protocol for a pragmatic phase IV stepped-wedge cluster-randomised trial, the CaPThai study

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Abstract

Background To end the tuberculosis (TB) epidemic, the WHO recommends implementing active case-finding to increase TB detection, as well as the provision of TB preventive treatment (TPT) in contacts of people with TB. However, the scale-up of both strategies remains limited in high TB-burden countries such as Thailand. Despite the country's highly decentralised healthcare system, significant inequalities remain in access to care, particularly in vulnerable populations. We designed an intervention study investigating the effectiveness and feasibility of a novel strategy combining active case-finding and the implementation of short-course TPT in households of newly diagnosed adults with TB in Thailand.

Methods This is a pragmatic phase IV stepped-wedge cluster-randomised trial conducted in 20 provincial hospitals (clusters). The study population comprises household members who were exposed within the last 3 months to adults with newly detected bacteriologically confirmed TB. The intervention combines an educational video to the index TB case, provision of an invitation card to household contacts for free TB screening at the facility, with a transport voucher, and support from village or urban health volunteers. Household contacts without active TB are offered TPT regimens according to age: 1-month rifapentine-isoniazid (1HP), 3-month rifapentine-isoniazid (3HP) or 3-month rifampicin-isoniazid (3HR). In the control phase, TB staff implement the current standard of care, including verbal information to persons newly diagnosed with TB on the need to screen their household contacts and provision of standard TPT. Hospitals shift from the control to the intervention phase every 3 months in four randomised sequences until all clusters apply the intervention. Generalised linear mixed models will be used to compare the intervention outcomes versus the standard of care, controlling for clustering and confounding by time.

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Discussion Active case-finding and systematic TPT in at-risk populations is currently limited in Thailand. This protocol incorporates pragmatic design features with a participant-centred approach to assess the effectiveness, feasibility and acceptability of a combined strategy including systematic screening of household contacts, active case-finding and TPT provision. If successful, this strategy will likely contribute to TB elimination in Thailand and beyond.

Trial registration The study is registered at ClinicalTrials.gov NCT05581212 on April 3rd, 2024, and is currently recruiting.

Keywords Tuberculosis preventive therapy (TPT), Active case-finding (ACF), Tuberculosis screening, Cluster-randomised trial (CRT), Stepped-wedge design (SW)

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Evaluation of a combined tuberculosis case-finding, treatment and prevention strategy in Thailand: study protocol for a pragmatic phase IV stepped-wedge cluster-randomised trial
Trial registration {2a and 2b}	ClinicalTrials.gov, NCT05581212
Protocol version {3}	English version 3.0/Thai version 5.0—22 March 2024
Funding {4}	Expertise France/L'Initiative VIH/Sida, Tuberculose, Paludisme—Grant No. 21SANIN207 French National Research Institute for Sustainable Development (IRD)
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Name and contact information for the trial sponsor {5b}	French National Research Institute for Sustainable Development (IRD) Cellule d'appui à la recherche impliquant la personne humaine (RIPH) en santé Email: cellule.riph@ird.fr
Role of sponsor {5c}	Role of the funding source L'Initiative had no role in the study design, data collection, data analyses, data interpretation or writing of the report. Role of the sponsor The French National Research Institute for Sustainable Development (IRD) had the role of scientific responsibility, project coordination and study monitoring.

Introduction

Background and rationale {6a}

Tuberculosis (TB) is a major, yet preventable, global health problem, with an estimated 10 million new cases worldwide in 2023, including 1.3 million in children and 820,000 in people living with HIV (PLWHIV) [1]. TB remains one of the top ten mortality causes worldwide [2].

According to the WHO, one third (2.9 million) of people with TB are not detected or reported by National TB Programmes in current practice. The WHO End-TB strategy strongly recommends active case-finding approaches in low- and middle-income countries (LMICs) to increase detection and treat prevalent and incident secondary case of TB, especially among children and PLWHIV [3, 4]. Household contact (HHC) investigation has been shown to have a high yield in increasing TB detection, but is labour-intensive and may be challenging in densely populated urban settings or slums [5]. A modelling study showed that HHC management could substantially reduce childhood disease and death caused by TB globally with an estimated 159,500 people with TB prevented every year in children <15 years [6, 7]. Further, a trial in Vietnam demonstrated a higher rate of case detection using active versus passive case-finding [8], thus underpinning the expansion of targeted active case-finding strategies among HHCs in high TB transmission settings.

One quarter of the global population is estimated to have (latent) TB infection (TBI) [7], and on average, 5–10% of people with TBI develop active disease over the course of their lives, thus contributing to the ongoing transmission [9]. HIV infection is the strongest risk

factor for progressing from TB infection to disease, with the overall annual risk estimated at 10% [10], particularly in children [11]. Similarly, people in the same household of people with TB are at higher risk of TB than individuals in the general population, particularly children aged less than 5 years [12]. Tuberculosis preventive treatment (TPT) is recommended in all HHCs of people with TB, particularly in children under 5 years of age and PLWIHV, to decrease the risk of developing active TB. Yet, over 69% of 50 million eligible HHC of people diagnosed with TB, including 15 million people living with HIV, did not access TPT as estimated by the WHO in 2024. A situation analysis in South East Asia region reported TPT coverage rates among HHC of 24% in 2024, thus 9% in people who initiated antiretroviral [1].

TPT has long relied on 6–12 months daily isoniazid [13–15]. In PLWHIV, isoniazid preventive therapy has been shown to reduce the overall risk of TB by an average of 30%, and there is strong evidence of its efficacy in association with antiretroviral therapy [16, 17]. The landscape of TPT has changed drastically over the last decade with the development of novel shorter regimens of isoniazid and rifapentine once-weekly over 3 months (3HP) or once-daily over 1 month (1HP). These regimens have been shown to be as safe and efficacious for TB prevention as 9 months of daily isoniazid in adults, particularly of the 3HP regimen regardless of HIV status [18–21], and in HIV-negative children aged 2–17 years [22, 23], with higher treatment-completion rate, better tolerability and improved safety (https://www.who.int/tb/features_archive/UNGA_report_on_HLMN_TB.pdf?ua=1, https://www.iom.int/news/united-nations-launches-thailand-migration-report-2019, [22]). TPT coverage among eligible individuals is one of the top 10 indicators to monitor progress on the advancement of the End-TB strategy at global and national levels [24].

Scaling-up an intervention in a TB high-burden setting

Thailand is one of the 30 high TB-burden countries, with an estimated TB incidence of 150 (114–191)/100,000 population and a total number of 87,789 new and relapse of people with TB reported in 2022. Children aged 0–14 years represent only 1% of all TB cases notified, and TPT coverage among children <5 years who are HHC of persons with infectious TB was just 6.4% in 2022 [25–27]. Systematic isoniazid preventive therapy for PLWHIVs has been introduced in the national health system but its implementation is limited and uneven. Yet, despite the considerable improvement in the health status of its population, there is still significant inequity with the burden of ill-health, particularly concentrated among the rural poor in the Northern, North-Eastern and Southern provinces, as well as in women and key vulnerable populations (e.g. PLWHIV, children, migrants and refugees) [28, 29].

In this context, the "Implementation of a new Strategic TB Case-Finding, Treatment and Prevention Public Health Pack in Thailand" (CaPThai) consortium aims to investigate the public health impact of a strategy combining active detection of TB among HHCs of adults with infectious TB, combined with the systematic provision of novel TPT regimens to exposed HHCs for whom TB is excluded. This study will provide evidence on the effectiveness of the proposed combined strategy, to increase TB case detection, accelerate the roll-out and scale-up of new WHO-recommended short-course regimens for TB prevention.

Objectives {7}

The overall objective is to evaluate the public health impact, acceptability and feasibility of an intervention combining active case detection and prevention of TB in HHCs of adult with confirmed TB in Thailand. The specific objectives are in the intervention versus standard of care phases: (i) to compare TPT initiation and completion among HHCs of infectious TB patients in the intervention vs. control phase; (ii) to evaluate the safety of short TPT regimens among HHCs; (iii) to compare the detection of TB and treatment uptake for active TB among HHCs; (iv) to evaluate the epidemiological impact of the combined intervention; (v) to investigate the feasibility of the intervention; (vi) to investigate the perceptions of providers and clients regarding the care and prevention of tuberculosis in HHCs.

Trial design {8}

CaPThai is a pragmatic phase IV stepped-wedge cluster-randomised trial (Fig. 1) comparing two phases: (i) the standard of care versus (ii) the investigational strategic intervention. The study will take place in 20 provincial hospitals. All hospitals will start the study under the standard of care (control phase) for at least 3 months. Then, five provincial hospitals, randomly selected, will switch to the intervention phase in four sequences occurring every 3 months (month 4, 7, 10 and 13), until all hospitals are exposed to the intervention. Each switch to intervention is preceded by a 1-month buffer period to train the staff on intervention procedures.

Methods: participants, interventions and outcomes

Study setting {9}

The Division of Tuberculosis at the Department of Disease Control of the Ministry of Public Health will conduct the trial in 20 provincial hospitals located across the country (May 2024 to September 2026). The hospitals have been selected based on a notification rate of >150 new persons diagnosed with TB in 2023. All administrative and healthcare providers in the hospitals and in the Office

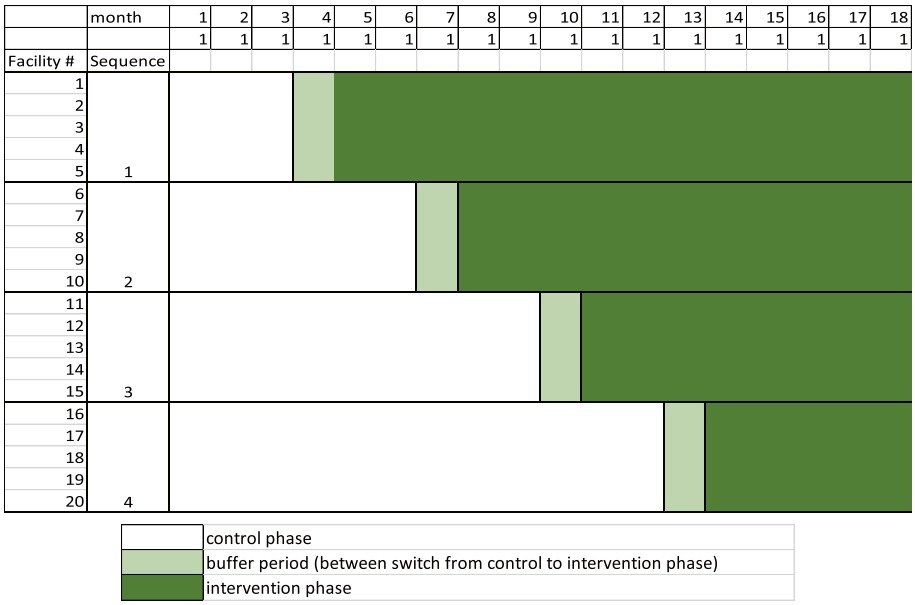

Fig. 1 Stepped-wedge design

of the Public Sector Development Commissions were duly informed and accepted to participate in the study.

Eligibility criteria {10}

The participants are adults, newly detected, bacteriologically confirmed, with pulmonary TB and the members, adults and children, of their household (HHC: household contacts), defined as living in the same household for at least 3 consecutive months. Participants are aged ≥18 years old with bacteriologically (smear/molecular test positive) confirmed drug-susceptible pulmonary TB, diagnosed in one of the study sites, and their HHC, children and adults. The people with TB who do not live in the catchment area (people living in districts, including village, within 50 km) of the study site, or those diagnosed with resistant TB, or who are incarcerated, are excluded from the study. HHCs will be excluded if they are on preventive or curative TB treatment, or who finished such treatment in the last 3 months.

Who will take informed consent? {26a}

Participants meeting the eligibility criteria and consenting to participate in the study will be included. Consent will be collected by the TB nurse at the study site, after informing participants about the study objectives, research implications, and the potential risks and benefits.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/a, no additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.

Intervention

Explanation for the choice of comparators {6b}

The standard of care is passive case-finding by informing people with TB that their HHCs should visit the health care facilities for TB screening and diagnosis and provision of either curative (6-month regimen combining isoniazid, rifampicin, ethambutol, pyrazinamide), or preventive treatment, most commonly 6–9 months of daily isoniazid (6–9H).

Intervention description {11a}

The intervention combines active case finding and TPT initiation among household contacts.

Active case-finding

At the facility, the people with TB will be sensitised on the importance of HHC investigation for detection and prevention of TB and stigma reduction through an educational video describing situations of people affected with TB. The people with TB will be asked to list all members of their HH, with indication of age, sex and duration living in the HH. Free screening at the study hospital will be offered to each HHC, using set screening invitation cards. Individualised screening cards will be provided to the people with TB for each HHC (or caregiver for those <18 years old). Reimbursement will be provided to cover transportation for the screening visit. In addition, the hospital TB nurse will organise a visit to the household from the urban/village health volunteers of each hospital catchment area within 2 weeks to counsel the HHC. The volunteers will enhance

awareness on the importance of TB screening for prevention and facilitate liaison with the study hospital.

TB screening

WHO recommended algorithms based on parallel screening with any TB symptom and chest X-ray, followed by Nucleic Acid Amplification Test (NAAT; molecular test, Xpert MTB/Rif Ultra), will be used to confirm or exclude active TB among HHCs [30–32]. Screening will include the following: a detailed history of TB exposure to the people with TB over the last 2 months; a detailed symptom review; a medical examination (including weight and temperature); a chest X-ray. X-ray reading will be performed by a trained radiologist in the hospital, with an indication of the presence of cavity, consolidation, enlarged hilar lymph nodes/lymphadenopathy, pleural effusion, miliary and number of affected lung zones; a NAAT performed on 2 expectorated sputa (or nasogastric aspirate or stool in children <5 years old unable to produce sputum sample) among HHCs with presumptive TB based on symptoms and/or X-ray. Pregnancy and HIV testing will be counselled and proposed when the pregnancy or HIV status is not known.

Active TB will be defined in adults (≥15 years old) as the presence of symptoms and/or radiological findings suggestive of TB, and molecular test positive; in children (<15 years old) as the presence of symptoms and radiological findings suggestive of TB, with or without MTB/Rif Ultra positive. HHCs detected with active TB will be eligible for curative treatment, while those in whom active TB is formally excluded, regardless of symptoms, will be eligible for TPT.

TPT

Preventive treatment will be initiated based on WHO recommendations: 3HR regimen daily dose for 3 months in children <2 years old (H: isoniazid, 15 mg/kg [10–20]; R: rifampicin, 10 mg/kg [7–15]); 3HP regimen weekly dose for 3 months in children 2–12 years old (H: isoniazid, 150 mg; P: rifapentine, 150 mg); and 1HP regimen daily for 1 month in adolescents aged ≥13 years and adults (H: isoniazid, 300 mg; P: rifapentine, 600 mg).

Criteria for discontinuing or modifying allocated interventions {11b}

TPT can be discontinued on decision from the hospital reference doctor and/or the TB nurse in case of (i) an adverse event (AE) or a serious adverse event (SAE) precluding the continuation of treatment, (ii) diagnosis of tuberculosis while on TPT or (iii) any reason justified by the safety condition of the HHC, particularly in children [33, 34]. For participants who discontinue TPT because of the occurrence of an AE/SAE, safety data will be collected until the resolution of their AE/SAE at the health facility. If TPT is discontinued due to the occurrence of TB, information on the treatment outcome will be collected from the national TB registry.

Strategies to improve adherence to interventions {11c}

People with TB and HHCs with active TB

The people with TB, and HHCs detected with active TB, will receive the recommended 2HRZE/4RH regimen (visits 1a, 1b); adherence to treatment will follow national recommendations (e.g. directly or video observed therapy). The people with TB and HHCs with active TB will not be followed-up within the study; the treatment outcomes will be abstracted from the TB register.

HHC eligible for TPT

TPT regimens will be provided (visit 1c) in several instalments as follows: 1HP: participants will initially receive 2 weeks of daily medication and will be asked to return to the hospital to receive a second prescription to cover the remaining medication, for a total of 1-month treatment (visit 2 to 3); 3HP: participants will receive medication for 4 weekly doses and will be asked to return to the hospital to receive the second and third allotments of 4 weekly doses at monthly intervals (visit 2 to 4); 3HR: the participants will receive medication for 4 weeks of daily doses and will be asked to return to the hospital to receive the second and third allotments at 4 weeks of daily doses at monthly intervals (visit 2 to 4). The nurse will inform the HHC of the importance of adherence and treatment completion and will directly observe the first dose of TPT intake on the day of prescription. At each visit, the nurse will ask the participants about the date the last dose was taken; any dose missed since the last visit; the occurrence of any event suggesting potential toxicity such as nausea, vomiting, reduced appetite, rash, jaundice (suggesting hepatotoxicity), numbness, tingling, burning or pain in lower extremities or difficulty walking (suggesting peripheral neuropathy); and the development of any new signs/symptoms since the last visit. In case of any symptom/signs suggestive of TB, the HHC will undergo a full medical examination with chest X-ray and NAAT. Participants will be reminded of their next scheduled visit by telephone call or SMS, 72 h before the due date. In case of missed appointment, a reminder call will be made and the visit rescheduled within the next 2 weeks. If the participants do not answer or fail to come to the rescheduled visit, the HHC will be considered non-adherent to the study protocol.

Final study visit

A final visit (visit 5) will be scheduled for all HHC started on TPT at 9 months from the first dose taken to assess their health condition. In case a HHC has symptoms suggestive of TB, he/she will undergo the same procedure as at initial screening (i.e. CXR, NAAT, HIV). The outcome of the investigation will be recorded. The HHC on TPT who miss a scheduled visit despite more than 2 reminders and who does not turn-up at the final visit will be considered lost to follow-up.

Relevant concomitant care permitted or prohibited during the trial {11d}

N/a, no relevant concomitant care and interventions are permitted or prohibited during the trial.

Provisions for post-trial care {30}

There is no financial expense to participate in this study. An insurance policy for the period of the study will be purchased by the sponsor to cover any unlikely harm directly resulting from participation in the study.

Outcomes {12}

The primary outcome is the proportion of HHC with no active TB initiated on TPT within 8 weeks of people with TB diagnosis. The secondary outcomes of interests are as follows: the proportion of HHC who complete TPT; the proportion of participants initiating TPT who discontinue treatment due to intolerance, adverse events or serious adverse events; the proportion of HHC with newly diagnosed TB started on curative treatment within 8 weeks of the people with TB; the proportion of HHC diagnosed with TB who complete TB treatment; the proportion of HHC receiving TPT who develop TB over the 9-month follow-up; the acceptability and feasibility of the intervention by providers and beneficiaries.

Participant timeline {13}

The participant timeline is displayed in Fig. 2.

Sample size {14}

HHCs identified by people with TB case will define the population for measuring the primary and some secondary endpoints. The sample size is computed accounting for the stepped-wedge design by incorporating a design effect of 1.25 and a coefficient of variation (k) of 0.30 [35, 36], assuming that 150 people with TB and 300 HHCs, with an average of two enumerating HHCs, are recruited at each hospital over an 18-month enrolment period. The distribution of HHC ages is expected to be 25%, 25% and 50% for those aged <5, 5–17.9 and ≥18 years, respectively. The calculation accounts for an 80% consent rate for participants with TB and assumes 20% will have no HHCs.

SCHEDULE	Enrolment	Allocation	Post-allocation			Close-out
Timepoint	T-1	T0	T1	T2	T3	T4
Enrolment						
Eligibility	X					
Consent	X					
Intervention						
Household contact registration	X					
Video display on TB screening and sensibilisation on stigma-reduction	X					
Invitation Card	X	X				
U/VHV visits	X	X				
Treatment initiation		X[1-3]				
1HP (adolescents ≥12 years old . and adults)			X	X[4]		X[4]
3HP (children 2-12 years old)			X	X	X	X[4]
3HR (children <2 years old)			X	X	X	X[4]
Assessments						
Medical history (TB, HIV)		X				
TB screening (Xpert, HIV, IGRA[5], Liver function, Pregnancy test[6], Chest X Ray)		X	X	X	X	X

HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; TB= tuberculosis; U/VHV=urban/village health volunteer
1 These visits take place within 4 weeks after T0, leaving necessary time for screening and collection of all results to assess screening outcome and decide on appropriate treatment.
2 TB curative treatment in case of confirmed TB Dx;
3 TB preventive treatment in case of TB formally ruled out
4 no treatment is dispensed at that visit
5 IGRA testing (blood): 5-18 years old/HIV- >18 years old, not required in HIV+ or <5years old
6 Pregnancy testing: women of childbearing potential and if date of last menstruation >6 weeks

Fig. 2 Participant evaluation

We hypothesise that the intervention will increase both uptake and completion of TPT. The proportion of HHCs who initiate TPT within 8 weeks of their household member diagnosis of TB was assumed to be 10% in the control phase, the sample size provides 90% power to detect an increase of 20% in the intervention phase, and 80% power when the coefficient of variation is 0.4. The sample size also provides 85% power to detect an increase in TPT treatment completion of 30% to 60% between the control and intervention phases, respectively. For the percentage of HHC newly diagnosed with TB initiated on treatment, the sample size provides 84% power to detect a relative risk (RR) of 1.75 (assuming 3.1% in the control phase) and 80% power to detect a RR of 2.0 within age subgroups.

Recruitment {15}

The trial will be conducted at selected provincial hospitals, and all eligible individuals will be invited to participate. TB nurses will review TB registers to identify all potentially eligible participants. All potential participants will be informed of the study's purpose; those who agree to participate will be enrolled by the TB nurses at each site. Participants will enter the trial on an individual basis and will be recruited continuously over an 18-month period. TB nurses will be trained via webinars regarding protocol details, clinical procedures, and both potential and actual challenges.

Assignment of interventions: allocation

Sequence generation {16a}

A covariate-constrained stratified-block procedure will be implemented in order to achieve balance in the characteristics of hospitals in both study phases over the four stepped-wedge sequences and computed with 10,000 repetitions. The randomisation will be stratified by a binary classification of the number of TB notifications at each hospital in the previous 12 months (high/low). Block randomisation will be used to ensure balance in the hospital TB notification classification over the four stepped-wedge sequences. Covariate restriction will be implemented to ensure balance between both study phases and four stepped-wedge sequences in terms of hospital geographical location and the number of non-Thai migrant TB notifications in the previous 12 months.

Concealment mechanism {16b}

Randomisation of the sequence in which hospitals will transition from control to intervention will be performed by the trial statistician prior to the start of enrolment, using R software version 4.3.3.

Implementation {16c}

The statistician will inform the investigators about the set of five hospitals that will move to the intervention phase at the start of each buffer period. The principal investigator will formally inform the hospital staff.

Assignment of interventions: blinding

Who will be blinded {17a}

Trial participants, TB nurses and the National TB Programme staff are blinded to which sequence each cluster will move to the intervention phase, to avoid bias in implementing new active case-finding strategies and introduction of TPT short regimens during the control phase.

Procedure for unblinding if needed {17b}

N/a, the study is a phase IV trial with minimal risks and constraints to participants; any circumstances under which unblinding is needed during the trial have been identified.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Cluster data

Aggregated data of people with TB registered and outcomes in the year before the intervention will be collected from hospitals as part of the baseline assessment before the intervention.

Individual data

To link people with TB with their HHCs, a HHC list, with a unique identifier by HHC, will be completed by the nurse. Individual data will be collected for each participant screened for the study including age, sex, relationship to the people with TB, presence of TB symptoms, tests performed and outcome, TB diagnosis and related treatment decision, eligibility for TPT, TPT initiation, tolerability, adherence, safety and treatment outcome. Validation checks will be performed prospectively on a regular basis, with oversight from the trial statistician. Captured study data will be transferred to an encrypted secure server and backed up daily. Data will be held in open formats (e.g. CSV) accessible using a range of software tools.

Plans to promote participant retention and complete follow-up {18b}

N/a, plans to promote participant retention and complete follow-up are described in the intervention section. There is no plan during the standard of care.

Data management {19}

Data will be directly entered in the electronic Research Electronic Data Capture (REDCap®) database by the TB nurses. Data quality will be ensured through real-time data entry validation. Each hospital will maintain

appropriate research records for this study. Most data collected in the study will be suitable for sharing in an anonymised format.

Confidentiality {27}

Confidentiality will be guaranteed by the REDCap® system, which will pseudonymise all patient data. After consent, participants will be given a unique study identification number. No information concerning subject data will be released to any unauthorised third party without prior written approval of the participant. Study records will be kept in locked cabinets, and computer records will be password protected. Access to study records will be restricted to specified study members and entities in agreement with the study delegation log. Study documents will be retained for a minimum of 10 years after study completion in a secured and safe area protected from risk of fire and humidity at the headquarters of the National TB Programme. Deviations from the protocol will be documented.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a, there are no plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The proportion of HHCs identified by the participants with TB and who initiate TPT within 8 weeks will be compared between the study phases. The intervention effect will be estimated at the individual level using a generalised mixed effects regression model, including random effects for cluster and household, and fixed effect adjustment for the stepped-wedge sequence time period. Secondary outcomes among HHCs that initiate TPT relating to TPT completion, and discontinuation due to adverse events, will be estimated using the same generalised mixed effects model specification.

TPT completion is defined as follows: 3HR: at least 68 of 84 doses within 120 days of starting treatment; 3HP: at least 11 of 12 doses within 120 days of starting treatment; 1HP: at least 23 of 28 doses within 40 days of starting treatment; 6H: at least 146 of 182 doses within 239 days of starting treatment [3].

The feasibility and acceptability outcomes will apply mixed methods that include reviewing research database, applying self-administered questionnaires, conducting observations and in-depth interviews, as well as organising focus group discussions.

Interim analyses {21b}

N/a, there are no interim analyses planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Analyses will be performed to adjust for possible differences in participants' characteristics between study phases. Subgroup analyses will examine intervention effects by age and sex, urban/rural area and migrant/non-migrant populations.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Missing data on TPT initiation would indicate that TPT was not initiated. For TPT completion, missing data may occur due to loss to follow-up of participants. Methods for handling missing data will consider including losses to follow-up as part of a composite outcome, or imputing missing data through multiple imputation or inverse probability weighting.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

CaPThai consortium supports research data and materials sharing. Individual data will be available on request and conditional to the signature of an access agreement in keeping with data protection best practices. Data outputs will be described on the collaborating institution websites including the London School of Hygiene and Tropical Medicine Data Compass. The project team will cite datasets in published paper, in compliance with https://www.ukdataservice.ac.uk/citethedata.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The overall management of the trial is ensured by the Project Management Group, composed of the lead project investigators from the participating institutions. The coordinating centre in Thailand is the Ministry of Health Division of TB, who will be responsible for overseeing the management of the trial, the day-to-day activities in the hospitals, and monitoring of study documents and source data verifications, assisted by the Institut de Recherche pour le Développement. Appropriate range and consistency check reports programmed into the REDCap® database will be reviewed regularly by relevant research staff.

Composition of the data monitoring committee, its role and reporting structure {21a}

Three committees will be established to provide advice to the Project Management Group on the project progress: (1) an independent Scientific Advisory Committee, composed of five researchers with high expertise in international clinical research, to provide advice on the relevance and scientific validity of research questions, study design and study implementation; (2) a Community Advisory Board to assist with study implementation and links with civil society and community engagement; and (3) a Safety Review Committee to review safety events during the study implementation period.

Adverse event reporting and harms {22}

Serious adverse events occurring in HHCs receiving TPT will be assessed by the TB nurse and reported. The TB nurse will refer the HHC to a referent clinician at the provincial hospital for advice and management. Serious adverse events will be reported to the Project Management Group and to the Independent Ethics Committee of Thailand (CREC: Central Research Ethics Committee).

Frequency and plans for auditing trial conduct {23}

The frequency of audit of the trial will be determined by a risk assessment of each site and the application of monitoring triggers or requests by the Independent Ethics Committee, the Project Management Group or the Scientific Advisory Committee.

The trigger will be determined by the participant enrolment rate, quality issues, trial site compliance or other trial site issues.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Important protocol modifications will be communicated to the relevant parties, which may include the study committees as well as the relevant ethics committees, trial registries and the sponsor.

Dissemination plans {31a}

The results of the study will be presented to authorities of the Ministry of Public Health in Thailand, as well as other national and international, public or private, organisations involved in TB control in Thailand. Results will be communicated through presentations at national and international conferences and publication of scientific articles in peer-reviewed literature. The scientific dissemination strategy will be reviewed by the Scientific Advisory Committee.

Discussion

Pragmatic clinical trials are used to evaluate the effectiveness of interventions in real-world settings, especially optimisation of health care practice and implementation of innovative technologies [37–39]. Pragmatic trials allow national authorities, local civil societies and international research agencies to collaborate in the preparation of recommendations to improve healthcare systems. However, challenges in transportability of findings necessitate robust methods to provide high-quality scientific evidence to public decision-makers [40–43].

The stepped-wedge cluster-randomised trial design is commonly used in the assessment of interventions being introduced as part of a change in policy. The design helps to alleviate logistical challenges by introducing the intervention in a phased approach [44]. During the last decade, the use of the stepped-wedge cluster-randomised trial design for infectious diseases interventions has expanded, particularly in low- and middle-income settings,[50–52] thus providing relevant, reliable and robust information that proved essential for worldwide policy decision-making [45–48].

The present study protocol incorporates pragmatic design features and assesses participant-centred outcomes, while respecting the rigour of clinical research, to support decision-making to implement a public health programme and update guidelines on tuberculosis detection and prevention in Thailand. If the intervention proves effective, it could serve as a model for tuberculosis control programmes in the Asian sub-region and beyond. Finally, this project will strengthen the capacity of health care providers in the 20 study hospitals.

Trial status

The current CaPThai protocol is version 3.0 of March 22nd, 2024. The trial received ethical approval from the Central Research Ethics Committee of Thailand on 11th January 2024, from the Ethics Committee of the London School Hygiene & Tropical Medicine on 22nd November 2023, and from the INSERM Ethics Evaluation Committee (CEEI/IRB) in France, on 13th September 2022. The trial opened on the 7th May 2024; all data collected from 7th May 2024 to 31 st July 2026 will be included in the analysis.

Abbreviations

1HP	One month of daily rifapentine plus isoniazid
3HP	Three months of weekly rifapentine plus isoniazid
3HR	Three months of daily rifampicin plus isoniazid
6H	Six months of daily isoniazid monotherapy
ACF	Active case-finding
ART	Antiretroviral treatment
BCG	Bacille Calmette-Guérin (vaccine)
BCP	Blister calendar pack
C	Control phase

CI	Confidence interval
CXR	Chest X-ray
DDC	Department of Disease Control
DTB	Division of Tuberculosis
eCRF	Electronic case report form
eTMF	Electronic trial master file
E	Ethambutol
FDC	Fixed-dose combination
FGD	Focus group discussion
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
H	Isoniazid
HHC	Household contact
I	Intervention phase
ICH	International Council on Harmonisation
IGRA	Interferon-gamma release assay
IRD	French National Research Institute for Sustainable Development
IPT	Isoniazid preventive therapy
IRB	Institutional Review Board
TBI	Tuberculosis infection
LSHTM	London School of Hygiene & Tropical Medicine
MOPH	Ministry of Public Health
MDR-TB	Multidrug-resistant tuberculosis
mITT	Modified intention to treat (population)
mWRD	Molecular WHO-recommended rapid diagnostic test
NAAT	Nucleic Acid Amplification Test
NGOs	Non-governmental organisations
NTP	National Tuberculosis Programme
NTIP	National Tuberculosis Information Program
OR	Odds ratio
PCF	Passive case-finding
PIS-CF	Participant information sheet and consent form
PI	Principal investigator
PLWHIV	People living with HIV
POC	Point of care
SOC	Standard of care
R	Rifampicin
REDCap	Research Electronic Data Capture (study eCRF)
RR	Relative risk
RR-TB	Rifampicin-resistant tuberculosis
SAE	Severe adverse event
SOP	Standard operating procedures
SRC	Safety Review Committee
SW-CRT	Stepped-wedge cluster-randomised trial
TB	Tuberculosis
TDOs	Trial data officers
THRF	Tuberculosis and HIV Research Foundation
TM	Trial manager
TMOs	Trial monitors
TPT	Tuberculosis preventive therapy
TST	Tuberculin skin test
U/VHV	Urban/village health volunteer
WHO	World Health Organization
WVFT	World Vision Foundation of Thailand
W4SS	WHO-recommended four-symptom screen
Z	Pyrazinamide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09532-7.

Supplementary Material 1.

Acknowledgements
We thank the Department of Disease Control of the Ministry of Public Health of Thailand for their support in the implementation of the project, as well as Expertise France/L'Initiative VIH/Sida, Tuberculose, Paludisme, for funding and close support. We thank the Scientific Advisory Board, Prof. Anneke Hesseling, Prof. Viroj Tangcharoensathien, Prof. Richard Chaisson, Prof. Virasakdi Chongsuvivatwong and Dr. Angela Crook. We thank Mrs. Usanee Ungcharoen and the staff of the Innovation and Research Unit of the Division of Tuberculosis for their implication in the preparation and follow-up of the project. Lastly, we thank Dr. Amandine Cournil, from the French National Research Institute for Sustainable Development (IRD), for establishing formal sponsoring.

Authors' contributions {31b}
TTS, project management, contributed to protocol development and wrote the first draft of the manuscript. JNY, conceived the social intervention proposal. DG, contributed to study design and protocol development. SB, developed the database and data management plan. SL, contributed to social intervention development. SO, database deployment and data management. NL, oversaw the pharmacovigilance procedures. MB, contributed to study design and to the development of the proposal. KF, lead trial methodologist. PK, contributed to protocol development and organised study implementation in Thailand. CL, conceived the study, led the proposal and protocol development.

Funding {4}
Funding by Expertise France L'Initiative VIH/Sida, Tuberculose, Paludisme—Grant No. 21SANIN207; French National Research Institute for Sustainable Development.

Data availability {29}
All authors had full access to the databases and had the final responsibility for the decision to submit for the publication.

Declarations

Ethics approval and consent to participate {24}
The Implementation of a new Strategic TB Case-Finding, Treatment and Prevention Public Health Pack in Thailand, CaPThai Study Protocol obtained the ethical initial approval by the Independent Ethics Committees of Thailand (CREC: Central Research Ethics Committee) No. COA-CREC108/2023 on January 11th, 2024, and UK (EC-LSHTM: Ethics Committee of the London School of Hygiene & Tropical Medicine) No. 28336 on October 24th, 2023.

Consent for publication {32}
A model consent form is available in Annex 1.

Competing interests {28}
The authors declare that they have no competing interests.

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Received: 25 July 2025 Accepted: 2 February 2026
Published online: 16 February 2026

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