'INSTEP2'

INCREASING NOTIFICATIONS OF TUBERCULOSIS FROM PRIVATE PRACTIONERS: A RANDOMISED CONTROLLED TRIAL

Statistical Analysis Plan

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(Protocol Version 1.0)

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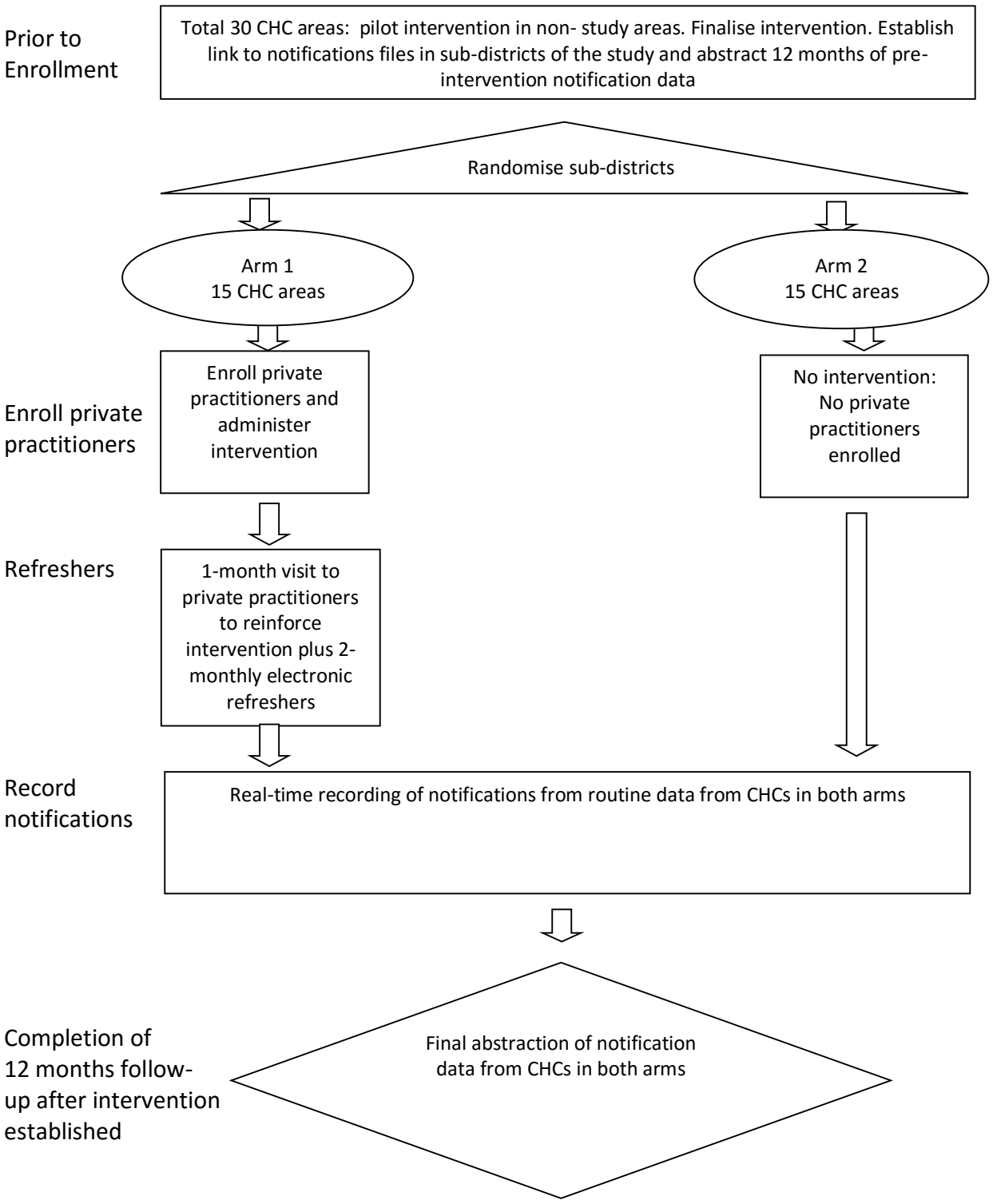
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Increasing notifications of TB cases from private practitioners (PP): a randomised controlled trial
Study Description:	This is a cluster randomised controlled intervention trial. The multi-component public health intervention will be administered to private practitioners in Community Health Centre (CHC) clusters. The change in the number of tuberculosis (TB) notifications over 12 months before, and 12 months after, the intervention will be compared between study arms. Hypothesis related to the Primary Efficacy Endpoint: A tailored intervention in PPs will increase TB notifications.
Objectives:	Primary objective: To evaluate whether a tailored intervention package increases notifications of TB from PPs in Bandung, Indonesia. Secondary objectives: (1) To calculate the proportion of referrals from PPs in the intervention arm that are actually diagnosed with TB; (2) To conduct a restricted analysis of the primary endpoint, limited to notifications of patients who live in the CHC area where they are notified.
Primary Endpoint:	The primary endpoint is the change in the number of notifications of TB from the 12 months before to the 12 months after the intervention is fully implemented. This change in the number of notifications will be compared between intervention clusters (n=15) and control clusters (n=15).
Study Population:	All those living in the 30 CHC clusters
Phase:	Pragmatic public health intervention efficacy trial.
Description of Sites/Facilities Enrolling PPs:	The intervention will be administered to PPs in areas around 15 CHCs (clusters), at their place of practice. PPs in the control areas will receive no intervention.
Description of Study Intervention:	(1) An electronic referral and notification system; (2) Education about signs and symptoms of TB and TB management; (3) An individualised practitioner plan for diagnostic and management pathways.
Study Duration:	3 years
PP involvement Duration:	2 years

1.2 SCHEMA


Prior to Enrollment
Total 30 CHC areas: pilot intervention in non- study areas. Finalise intervention. Establish link to notifications files in sub-districts of the study and abstract 12 months of pre-intervention notification data
Randomise sub-districts
Arm 1
15 CHC areas
Arm 2
15 CHC areas
Enroll private practitioners
Enroll private practitioners and administer intervention
No intervention: No private practitioners enrolled
Refreshers
1-month visit to private practitioners to reinforce intervention plus 2-monthly electronic refreshers
Record notifications
Real-time recording of notifications from routine data from CHCs in both arms
Completion of 12 months follow-up after intervention established
Final abstraction of notification data from CHCs in both arms

1.3 BACKGROUND

The 2014/15 TB prevalence survey in Indonesia estimated that there were 1 million cases of TB, and over half of the TB cases were not notified. The huge private sector in Indonesia, comprising an estimated 70,000 practitioners, provides over 50% of health care but notifies less than 10% of all diagnosed TB cases. TB patients managed in the private sector are often treated sub optimally and have poorer outcomes. The majority of people with symptoms of TB initially engage private practitioners (PPs), but 80% of the facilities they attend cannot diagnose TB. As part of advancing Public-Private Mix (PPM) the government made TB notification mandatory in 2016, but intervention is likely to be needed for notifications to increase substantially.

PPs are medically trained general practitioners or specialists. They work outside government Community Health Centres (CHC), either in solo practice or private clinics. When they diagnose TB patients, they are supposed to refer and notify them to the CHC or another DOTs treatment facility. Some have an agreement with the CHC to continue to treat their patients using free TB drugs supplied by the government. We have identified 245 of 1200 PPs in the 30 study areas that had diagnosed at least 1 TB case in the previous 3 months (total n=870 TB cases) - less than 20% had been notified.

The primary goal of this randomised controlled trial is to increase notifications of TB by PPs through a tailored intervention.

1.4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS/KEY MEASURES
Primary	
To evaluate whether a tailored intervention package increases notifications of tuberculosis (TB) by private practitioners in Bandung, Indonesia.	The primary endpoint is the change in the number of notifications of TB from the 12 months before to the 12 months after the intervention is fully implemented.
Secondary objectives of trial	
To calculate the proportion of referrals from PPs in the intervention arm that are actually diagnosed with TB	The proportion of referrals from PPs in the intervention arm that are actually diagnosed with TB
To conduct a restricted analysis of the primary endpoint, limited to notifications of patients who live in the CHC area where they are notified.	The same as primary endpoint, restricted to notifications of patients who live in the CHC area where they are notified.

1.5 STUDY DESIGN

This is a cluster randomised controlled trial of a multi-component public health intervention to increase notifications of TB from PPs in one city, Bandung, in Indonesia. Clusters are CHC areas.

1.5.1 Population

Of 73 Community Health Centre (CHC) areas in Bandung, 30 were randomly selected for the INSTEP study, proportional to their catchment population's size, and will be included in the RCT. There are no exclusion criteria. The study population consists of all the people who may visit a PP in any of the study areas during the during the year before and the year after the intervention – outcome is measured on all people who visit a PP in a study area, are diagnosed with suspected TB and reported to the CHC.

1.5.2 Randomisation

Using the randomly selected areas from the previous INSTEP study, we will randomly select 15 areas as intervention areas, repeating the randomisation 100 times. From this we will select the 10 allocations that meet the criteria of i) including having the least number of adjacent CHC areas between intervention and control arms, to minimize contamination between the arms, and ii) balancing by CHC numbers of TB cases diagnosed per annum. Then we will randomly select the final allocation from those 10.

1.5.3 Study interventions

The intervention will be administered directly to PPs in sub-districts randomised to the intervention arm. All medically qualified PPs in the CHCs in the intervention arm who reported having diagnosed at least one TB case in the past 3 months when visited in the INSTEP study will be eligible for the intervention. We expect around 80% of approached PPs will be willing to participate in the study. The intervention consists of: i) an electronic referral and notification system; ii) education; iii) an individualized plan for each PP for diagnosis and management; iv) a 1 month follow-up visit; and v) a 2-monthly electronic reminder/refresher.

The CHCs in the control arm will be informed about the study and asked, through the National TB Control Programme, to make their notification data available and their willingness will be recorded. No intervention will be given to PPs in the control arm.

1.5.4 Outcome measures

Primary outcome measure

- The rate of TB notifications to the CHC by PPs for each CHC.

Secondary outcome measures:

1. The proportion of referrals from PPs to a CHC which are confirmed to TB for each CHC
2. The rate of TB notifications to the CHC by PPs for patients who live in the CHC area where they are notified.

Data abstraction from routine TB notifications will be done by trained researchers. The 12-month period before intervention commences will be defined clearly and data abstraction will take place as soon as possible at the end of this period. The 12-month follow up period will also be defined clearly. The start date will be immediately after the last PP to receive the intervention has had their 1-month follow up visit. Data abstraction will be done as soon as possible after this 12-month period is completed.

2 STATISTICAL ANALYSIS

2.1 GENERAL APPROACH

The primary analysis will be intention-to-treat, where all patients notified by intervention and control PPs to a CHC will be included. Analysis will be carried out at the cluster level, taking into account correlations

within a cluster. 95% confidence intervals will be calculated and a significance level of 0.025 (one-sided) will be used. Statistical analyses will be carried out in Stata.

2.2 BASELINE DESCRIPTIVE STATISTICS

Study arms will be compared on baseline characteristics, including demographics of the PPs and the diagnosed TB cases, using descriptive statistics. No inferential statistics will be used.

2.3 PRIMARY ANALYSIS

For the primary trial analysis we will estimate the rate ratio comparing TB notifications in the intervention and control groups post-intervention using generalized estimating equations, adjusted for pre-intervention notification rates. The model will be fit to repeated measures of the rate of TB notifications for each CHC (pre- and post- intervention) with a treatment by time interaction, a log link, and Poisson errors, with robust standard errors to allow for over-dispersion. A contrast statement will be used to obtain the rate ratio estimate, 95% confidence interval and p-value.

2.4 SECONDARY ANALYSES

1. The proportions of true TB cases among the reported TB cases will be compared in post-intervention in the intervention and control arms using generalized estimation equations. The model will be fit to repeated measures of the proportions of true positive TB notifications for each CHC (pre- and post- intervention) with a treatment by time interaction, a log link, and Poisson errors, with robust standard errors to allow for both the binary data and over-dispersion. A contrast statement will be used to obtain the rate ratio estimate, 95% confidence interval and p-value.

2. The primary trial analysis will be repeated excluding patients who were notified by a PP from a different CHC to their area of residence.

2.5 SAMPLE SIZE JUSTIFICATION

Less than 10% of PPs work privately in more than one CHC area. Those who also practice within the public system should not affect notifications from that public system, as it has a high notification rate (>95%) already.

While the majority of notified TB patients are diagnosed and treated in their own CHC area, a number are diagnosed outside of their 'home' CHC area (up to 35%; INSTEP study). Those from a different CHC area will have an approximately 1 in 5 chance of being from another intervention area, 1 in 5 chance of being from a control area, and 3 in 5 chance of being from a non-study CHC area (n=43 non-study CHC areas within Bandung). Therefore 'contamination' of the intervention into control areas is estimated to be <10% (35% x 1/5 = 7%).

We will have data on the number of individuals from CHC areas outside the intervention areas who are notified by PPs in the intervention arm. Any change in notifications in the control arm will also provide insight into contamination. The primary analysis will compare the change in total number of notifications of patients between intervention and control areas.

Assuming (1) PPs in each arm diagnose at least 500 TB patients in 12 months (INSTEP data); (2) 65% of PP TB diagnoses are patients from their CHC area and 35% are from outside their area; and (3) a 15% baseline notification rate changing to 50% post-intervention in the intervention arm: PP notifications in the control arm areas will change from 75 to 87 notified cases while the change will be from 75 to 201 cases in the intervention arm. Total notifications (adding 475/arm from non-PP) will change from 550 to 562 and 550 to 676 respectively.

Taking the above into account, we will have approximately 90% power to detect a rate ratio of 1.2 (676/562) at the p=0.025 level (one sided).

3 DATA MONITORING COMMITTEE

Safety oversight by an independent Data and Safety Monitoring Committee (DMC) will not be required for this public health intervention trial. However, an internal Data Monitoring Committee will be established to oversee the study, focused on data quality.

4 DATA HANDLING AND QUALITY ASSURANCE

A quality management plan will be developed to describe a CHC's quality management. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be automatically generated on a weekly basis and any quality issues identified will be reviewed by the DMC and a plan put in place for resolution.

Following written Standard Operating Procedures (SOPs), visiting investigators (Dr Sue McAllister or substitute) will verify that the trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol. The investigational site will provide direct access to all source data/documents, and reports for the purpose of the verification visits.

Clinical data, and clinical laboratory data, will be entered into REDCAP electronic database. The data system includes password protection and will be checked automatically for data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

5 CONTENT OF FINAL STATISTICAL REPORT

- One page outline of study design
- Major protocol changes
- Recruitment and randomisation of CHCs including
    - reasons for ineligibility
    - number recruited and randomised
- Baseline characteristics of CHCs (population, TB notifications in the last 12 months)
- Baseline characteristics of PPs (age, gender, self-reported TB notifications in the last 3 months)
- Days between randomisation and initiation of intervention at the intervention PPs.
- Intervention delivery including
    - Proportion randomized to intervention who received each component
    - Proportion receiving 1 month visit
    - Adherence to intervention at 1 monthly visit (?"pre-determined indicators")
    - Proportion receiving 2 monthly follow-up electronic refreshers
    - Adherence to intervention at 2 monthly visits (?"pre-determined indicators")

    - Withdrawal from intervention of PP, reasons for withdrawal
    - Loss to follow-up of PP, description of determination of LTFU
    - Intervention related events including app malfunction and loos of network connection for periods of time
- Comparison of characteristics of participating and non-participating intervention PPs (age, gender, self-reported TB notifications in the last 3 months)
- Description of outcome data
    - Notification periods before and after intervention by PP (duration, calendar time)
    - Description of notified patients (age, gender, CHC, sputum status, basis of TB diagnosis)
    - Proportions of definite/probable/possible /Not TB
- TB notification rates before and after intervention (Table, Figure showing individual change by CHC)
- Primary analysis – TB notification rate ratio in the year after intervention (for 12 months from X months after randomization) adjusted for baseline notification rate
    - Estimate, 95% confidence interval and p-value from Poisson regression
- Secondary analysis
    - Relative risk comparing the proportion of al TB notification which are true TB cases in intervention and control groups (estimate, 95% confidence interval, p-value)
    - TB notification rate ratio as for primary analysis but excluding patients who were notified by a PP from a different CHCN to their area of residence

DMC report

Safety oversight by an independent Data and Safety Monitoring Committee (DMC) will not be required for this public health intervention trial. However, an internal Data Monitoring Committee will be established to oversee the study, focused on data quality.

The report will include:

- One page outline of study design
- Major protocol changes
- Recruitment and randomisation of CHCs including
    - reasons for ineligibility
    - number recruited and randomised
- Baseline characteristics of CHCs (population, TB notifications in the last 12 months)
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