RESEARCH PROTOCOL **RP-PG-0407-10340**

Title: **TB-REACH**
Improving the Management and Control of Tuberculosis among Hard to Reach Groups

Protocol Version#: 4

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List of abbreviations:

TB -Tuberculosis
LTBI -Latent TB Infection
IGRA -Interferon Gamma Release Assays
DOT -Directly Observed Therapy
ETS -Enhanced Tuberculosis Surveillance
HPA -Health Protection Agency
MXU -Mobile X-ray Unit
RIS -Radiology Information System

AIMS AND OBJECTIVES:

To improve the management and control of tuberculosis (TB) among homeless people, prisoners and problem drug users (hard to reach groups) by developing and evaluating the effectiveness of novel approaches to case finding and management tailored to the needs of these groups. This is with a view to improve access to care and treatment outcomes for the hard to reach patients. This will inform service commissioning and augment TB control in London throughout the programme and beyond. The findings will be generalisable to cities in low prevalence countries.

BACKGROUND:

Rates of tuberculosis (TB) in London have doubled in the last 2 decades and are now highest amongst homeless people, prisoners and drug and alcohol users (hard to reach groups). While most people who are infected with the organism mycobacteria which causes TB will never go on to develop TB, hard to reach groups may be at much greater risk of infection and progression to active disease. Tuberculosis control is founded on patient completing an effective course of treatment for a minimum of 6 months plus early diagnosis of disease to reduce the risk of onward transmission to others. Hard to reach groups do not engage well with traditional hospital-based services. Their lifestyle factors mask clinical symptoms of disease and complicate treatment through insecure housing tenure, addiction issues and frequent contact with the criminal justice system. Directly observed therapy (DOT) where a responsible adult watches the patient swallow every dose has been recommended internationally as a standard of care for hard to reach groups but is not widely used in London. Tuberculosis amongst hard to reach groups now presents an immense public health challenge.

This project investigates a series of linked interventions which span the care pathway. We will 1) Measure how common latent TB (asymptomatic) infection is, and how frequently it progresses to active disease using a new blood test; 2) Assess the effectiveness of chest X-Ray screening for tuberculosis in prisons and measures to improve the uptake of screening in homeless shelters; 3) Develop and evaluate a rapid diagnostic service to ensure suspected cases are investigated promptly; and 4) Compare patient centred DOT arranged by a specialist community team with standard DOT developed by hospital. These interconnected components will generate new information to better understand TB transmission within and from these groups and the cost effectiveness of interventions.

RESEARCH PLAN:

We propose a series of interconnected projects to evaluate novel interventions for hard to reach TB patients.

Sub-study 1: Latent TB Infection (LTBI)
Cross sectional survey of latent TB (asymptomatic) infection using Interferon Gamma Release Assays (IGRA) testing, HIV, and hepatitis B and C.

Long term follow up using data linkage with national Enhanced Tuberculosis Surveillance (ETS) at the Health Protection Agency (HPA) will be established to assess the risk of progression to active disease.

Sub-study 2: Strengthening TB control in Prison
Evaluate the effectiveness of a new prison X-ray screening system using teleradiology network of static digital X-ray units to reduce the risk from TB in prisons.

Case-comparison study of TB cases: comparing prisoners with TB actively identified via the static X-ray screening versus prisoners with TB passively identified through other means (excluding the existing Mobile X-ray Unit (MXU) screening).

Long term follow up through data linkage with national ETS will also be established.

Sub-study 3: Improving uptake of mobile X-ray screening for tuberculosis
Cluster randomised controlled trial evaluating impact of peer education to increase uptake of MXU screening for TB among homeless populations.

Sub-study 4: Promoting rapid diagnosis
Establish and evaluate a rapid diagnostic service (Cepheid's Xpert® MTB/RIF) as a point of care test in the community to ensure suspected cases of TB in hard to reach groups are investigated promptly and optimally managed. This widely used polymerase chain reaction (PCR) based test detects the presence of *Mycobacterium tuberculosis* in sputum samples and identifies resistance to Rifampicin, a reliable surrogate marker of strains that are multidrug- resistant (MDR-TB).

Sub-study 5: **Virtually Observed therapy (VOT) versus Directly Observed Therapy (DOT)**
Individually randomised controlled trial comparing virtually observed therapy (VOT) arranged by a specialist community team using internet based technologies with standard directly observed therapy (DOT) arranged by a TB Service to support treatment adherence.

Sub-study 6: Cost effectiveness
Development of a dynamic transmission model to predict public health impact of the interventions and inform economic analysis comparing costs to the savings made through averting future cases.

STUDY PROCEDURES:

This programme is largely health services research and involves vulnerable and marginalised populations. Studies will be submitted for MREC approval.

The research studies will involve:

SUB-STUDY 1. Latent TB Infection (LTBI)

1. Primary objective:
   - To determine the prevalence of latent TB infection among prisoners, drug users and homeless people in London in order to inform a mathematical model (sub-study 6) of public health impact and cost effectiveness of screening (using IGRA testing) and treatment of LTBI among these hard to reach group.

2. Secondary objectives:
   - To determine the prevalence of co-infection with HIV, and hepatitis B and C in hard to reach groups in London and how this vary according to demographics and life style risk factors such as prison history, alcohol and drug use.
   - To measure the risk of progression from latent TB to active disease in hard to reach groups in London and how this varies according to demographics, co-infection with HIV, hepatitis B and C and other life style risk factors such as alcohol and drug user.

Setting:
1. HMP Pentonville prison will be the main site of recruitment for prisons. We may also include other prisons that are part of the Department of Health funded TB screening service who have established local arrangements for management of blood borne viruses, if necessary.
2. Homeless hostels alongside the NHS routine radiologic screening programmes for active tuberculosis and blood borne viruses by “Find&Treat” team.

Target population: Prisoners and homeless people (who will include many drug users) with informed written and verbal consent.

Inclusion and exclusion criteria: Hard to reach groups (homeless people and prisoners) 16 years of age or older in London who have consented to NHS-run radiographic screening for active tuberculosis in prison

and homeless hostel settings are eligible to participate. Those under the age of 16 are excluded from participating.

Measurements:

1. Baseline questionnaire covering socio-demographic (such as age and gender) and risk factors for TB (such as history of imprisonment, history of drug and alcohol use, history of homelessness, country of birth, and previous contact with TB) will be administered.
2. We will use whole venous blood samples to test for TB infection, HIV, and Hepatitis B and C.
   - Prevalence of TB infection will be measured using the IGRA assay test which exploits the body's immune response (T cells) to determine whether a person has currently or previously been infected with Mycobacterium TB. The patient's blood is stimulated with synthetic antigens and the amount of the cytokine, gamma interferon produced in response to this is measured.
   - Prevalence of HIV and Hepatitis co-infection will be measured because the risk of latent infection progressing to active disease is substantially higher in HIV infected people and because preventative treatment for latent TB infection can lead to sometimes fatal hepatoxicity (which may be more likely in those with viral hepatitis).

Sample size: 3,000 individuals (1500 from prison settings, 1500 from homeless shelter settings).

Participant follow-up procedure:
Results will be fed back through offender health and community blood borne virus teams so that timely and appropriate clinical action is taken. We will match those screened with national ETS data using previously established methodology (modified SOUNDEX codes - anonymised codes derived from names, and dates of birth) to establish rates of progression to active disease.

The referral protocol is as follow:

Referral Protocol

Refer all BBV positives to BBV services within prison and alongside residential hostels
Refer all haemoptysis to TB services regardless of other results
Refer all with X-ray suggestive of active TB to TB services regardless of other results

	TB Referral		
LTBI Test Results	**HIV positive**	**CXR Normal HIV negative**	**CXR Old HIV negative**
Any positive IGRA	TB Referral	Inform and advise	TB Referral
Indeterminate IGRA	TB Referral	Inform and advise	TB Referral
All negative	No TB referral	No action	No action

BBV:Blood borne virus
IGRA: Interferon Gamma Release Assays
LTBI: Latent TB (asymptomatic) infection

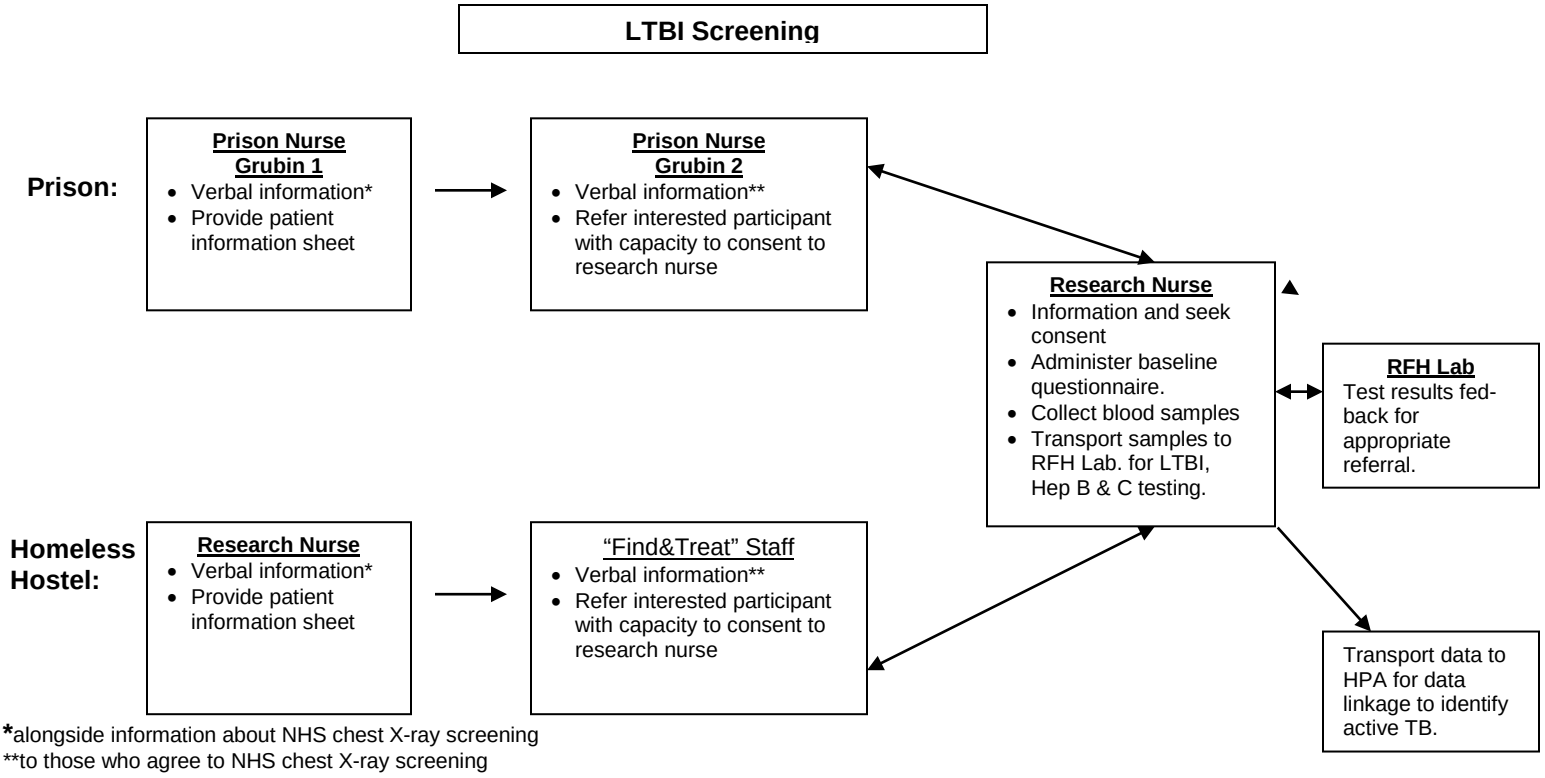
Economic evaluation: We will use the measured levels of latent TB infection, and blood borne viral infections, rates of progression to active TB, the results of previous studies on adherence and adverse reactions to chemoprophylaxis and the output of the mathematical model (study 6) to estimate potential public health impact and cost effectiveness of different approaches to screening and treatment for latent infection.

Duration and practical procedure: Testing will be conducted at the Royal Free Hospital (RFH) by the laboratory scientist employed for the study. The blood samples will be labelled with necessary patient identifiers as for clinical specimens and transported to the laboratory by the research nurse.

1. We will liaise closely with offender health services to coordinate testing to be around the same time routine X-ray screening is being performed. The prison screening will be completed by year 3 of the programme.

2. Testing during the Health "MOT" sessions (alongside "Find&Treat" screening) will take place throughout the study and will be offered to all new and existing clients (extensive screening for blood born viruses is already conducted routinely by BBV teams working alongside the unit).

Sub-study 1



*alongside information about NHS chest X-ray screening
**to those who agree to NHS chest X-ray screening

SUB-STUDY 2. **Strengthening TB control in prisons**

1. Primary objective: To determine the
   - Yield of screening and impact of infectiousness at diagnosis.

2. Secondary objectives: To measure
   - Prevalence of tuberculosis in those screened.
   - Screening coverage (proportion of eligible prisoners screened).
   - Diagnostic and treatment outcomes (including use of isolation resources, use of DOT, hospitalization and treatment completion) of people referred for investigation following an X-ray suggestive of active tuberculosis.
   - Future risk of tuberculosis.
   - Prevalence of old fibrotic lesion.

Setting: London prisons (Brixton and Pentonville) that are part of the Department of Health funded static digital X-ray programme for routine screening of prisons for TB.

Target population: Data extraction on new prisoners at participating prisons in London. This study does not involve active participation of subjects.

Inclusion and exclusion criteria: Radiologic data on all new prisoners screened upon reception into the prison or soon thereafter through the new digital X-ray programme at participating prisons will be included in the study.

Measurements:
The digital chest X-ray along with information on the patient will be stored electronically in a Radiology Information System (RIS) and transferred via a teleradiology network for reading offsite at Whittington hospital. X-ray changes will be classified according to an internationally accepted TB screening standard.

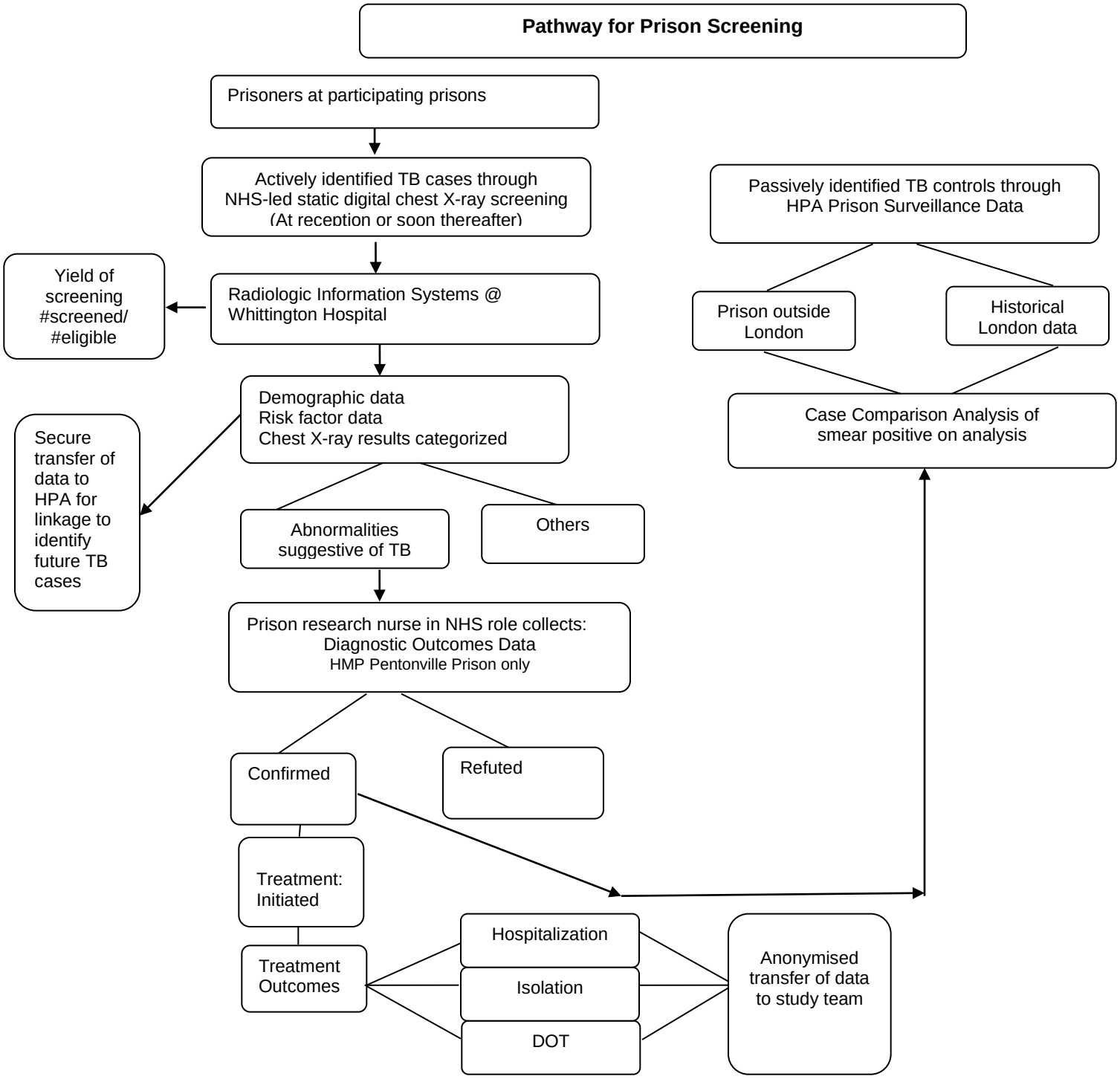
1. We will incorporate collection of baseline socio-demographic and risk factor data (including age, gender, ethnicity, country of birth, previous TB, recent contact with TB, history of drug and alcohol use, history of homelessness, as will as clinical symptoms at time of screening) into the screening process to be collected on the RIS and transferred with the X-rays

2. We will estimate the screening coverage, yield of screening, diagnostic and treatment outcomes i.e., proportion of eligible prisoners screened, prevalence of tuberculosis among those screened and the proportion of those screened who are:
   - Referred for further investigation
   - Investigated to confirm or refute diagnosis of tuberculosis
   - Diagnosed as tuberculosis
   - Infectious smear positive sputum at diagnosis
   - Started on tuberculosis treatment
   - Complete tuberculosis treatment
   - Required hospitalization, use of isolation resources and DOT

3. We will compare smear positive, culture positive and symptom at diagnosis in cases identified through screening with controls identified passively. Controls will be identified from HPA prison surveillance system from prisons outside London with no screening and historic controls from within London prisons prior to the new screening programme.

4. We will estimate the accuracy and performance of digital X-ray screening by periodically matching screening results with enhanced surveillance data. This will enable estimation of:
   - Prevalence of old fibrotic lesions and future risk of TB in prisoners with X-ray abnormalities suggestive of previous and potentially untreated disease.
   - Future risk of TB in prisoners with no changes suggestive of active or previous TB.
   - Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Sub-study 2


Pathway for Prison Screening
Prisoners at participating prisons
Actively identified TB cases through NHS-led static digital chest X-ray screening (At reception or soon thereafter)
Passively identified TB controls through HPA Prison Surveillance Data
Yield of screening #screened/ #eligible
Radiologic Information Systems @ Whittington Hospital
Prison outside London
Historical London data
Demographic data
Risk factor data
Chest X-ray results categorized
Case Comparison Analysis of smear positive on analysis
Secure transfer of data to HPA for linkage to identify future TB cases
Abnormalities suggestive of TB
Others
Prison research nurse in NHS role collects:
Diagnostic Outcomes Data
HMP Pentonville Prison only
Confirmed
Refuted
Treatment: Initiated
Treatment Outcomes
Hospitalization
Isolation
DOT
Anonymised transfer of data to study team

Sample size:

200 cases for the case comparison study (100 cases actively identified through the new screening and 100 controls passively identified in prisons where screening is not taking place from national ETS data). These will arise from around 50,000 prisoners screened by the NHS in prisons (around 25,000 screens in London per year).

Participant follow-up procedure: Outcome data will be collected on referrals from HMP Pentonville prison where our research nurse will be mainly based. This information will be collected by prison research nurse in NHS role.

Economic evaluation: We will use the results to provide parameters for the dynamic mathematical model described in study 6. This model was developed for a DH funded evaluation of MXU screening and allows the number of cases averted through early case detection to be estimated into the future. The costs of the screening programme and of investigating referred prisoners will be combined with the costs saved through averting cases to develop an overall incremental cost effectiveness ratio (ICER) for the programme. We will also describe the cost-effectiveness of providing chemoprophylactic treatment for those with radiographic abnormalities suggestive of previous TB infection.

Duration and practical arrangements: This part of the study will continue for 4 years. We will liaise closely with Offender Health Services during the set up of the prison screening programmes to establish routine data collection mechanisms using the RIS.

SUB-STUDY 3. Improving uptake of X-ray screening for tuberculosis

1. Primary objective:
   - To determine the effect of peer educator on uptake of MXU screening.

2. Secondary objective:
   - None

Settings: Hostels for homeless people within London being offered NHS-led mobile X-ray screening. Hostel selection will be stratified by:

- Historical uptake data on previous uptake of screening (i.e., poorly performing hostels compared with hostels with similar low uptake and vice versa.
- Size of hostel (small - 20-40 residents, medium - 40-69 residents versus large - >70 residents).
- Average length of stay

Pairs of hostels that are similar on the basis of these characteristics will be randomised to intervention (use of peer educator) and control (normal practice by use of “Find&Treat” team)

Target population: Residents of homeless hostels who have not been screened in the 6 months prior to onset of study.

Inclusion and exclusion criteria: Hostels within London being offered NHS-led mobile x-ray screening

Measurements: Aggregate data comparing uptake of the offer of screening between intervention and control arm using the bed-list as the denominator.

- Number of residents eligible for screening will be determined from hostels’ records.
- Number accepting screening will be determined from the MXU screening records.

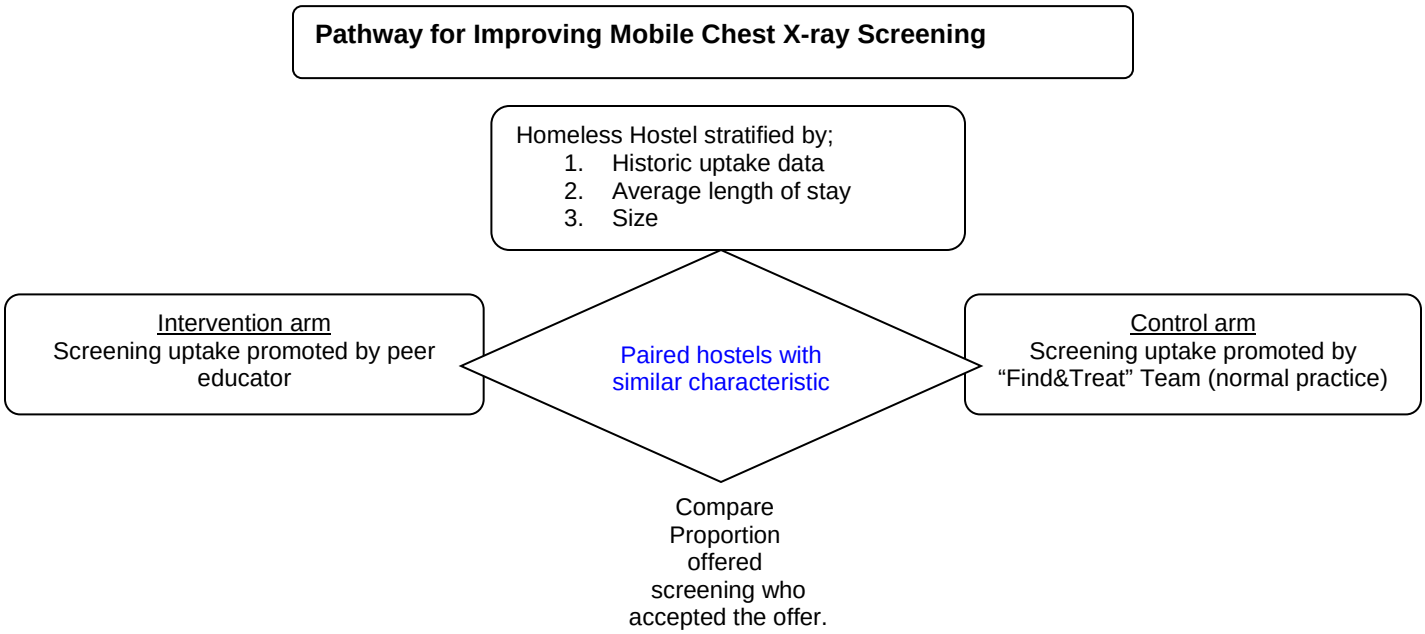
Sample size: 2800 (1400 residents from 20 hostels in each arm) in London.

Participant follow-up procedure: Not applicable

Economic evaluation: We will use the results to inform mathematical model described in study 6.

Duration and practical arrangements: This study will be completed over a two year period.

Sub-study 3



SUB-STUDY 4. Promoting rapid diagnosis

1. Primary objective:
   - To determine whether the introduction of Cepheid Xpert® MTB/RIF (a PCR based test) to confirm active TB and rifampicin resistance in the field can reduce loss to follow-up, time to onset of optimal treatment as well as enable more appropriate use of hospital and isolation resources.

2. Secondary objective: To compare outcomes in those investigated by the rapid diagnostic service (intervention arm) compared to normal practice (control arm) i.e., those who had TB, started TB treatment, completed their full course of treatment and were treated or admitted in hospital for TB. As a long term outcome measure, the proportion of pulmonary smear, PCR and culture negative cases in each group who developed active TB will be identified through data linkage to the national TB surveillance system and compared.

Setting: A rapid diagnostic service as a near patient test in community settings alongside the mobile X ray screening unit (MXU) run by Find&Treat, an NHS pan-London specialist community outreach team.

Target population: Hard to reach patients with abnormal chest X-rays suggestive of active TB identified through MXU screening at hostels for homeless people and drug and alcohol services across London. These patients will be randomised into either an intervention arm or control arm and recruited with informed written and verbal consent.

Inclusion and exclusion criteria: Any hard to reach patients accessing the MXU with radiological changes suggestive of active pulmonary TB. Persons not able to produce a sputum specimen and persons who refuse to participate will be excluded.

Measurements: All the samples will get sputum smear microscopy and culture to identify the presence of *Mycobacterium tuberculosis*. The key difference from normal practice is the use of Cepheid's Xpert® MTB/RIF, a rapid PCR test on the MXU (on patients in the intervention arm) rather than as a laboratory based test to identify *Mycobacterium tuberculosis* and resistance to Rifampicin in sputum samples - a reliable surrogate marker of strains that are multidrug-resistant (MDR-TB).

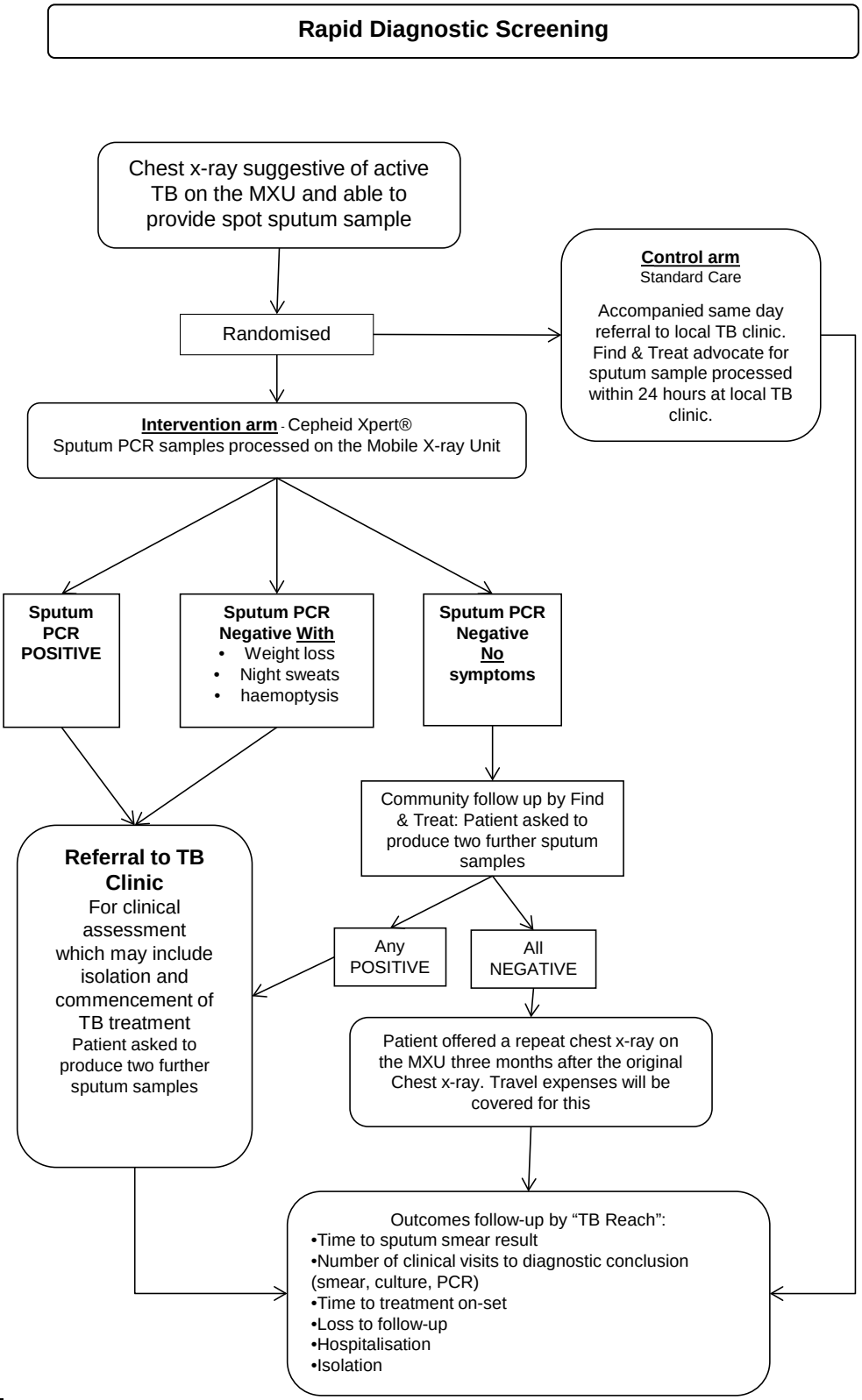
Sample size: 40 patients in each arm.

Participant follow-up procedure: As per current practice, all hard to reach suspected tuberculosis cases referred from the MXU screening unit will be tracked to diagnostic conclusion across London by Find&Treat. This follow up includes time from reporting of an abnormal chest X ray to confirmation of diagnosis (based on PCR and culture test results), time to sputum smear positive test results, loss to follow up prior to diagnostic conclusion, hospitalisation and isolation. We will compare these outcomes on patients in each arm.

Economic evaluation: The mathematical model will be used to calculate the number of infections and active cases averted through reducing loss to follow up associated with diagnostic delay. The value of these averted cases will be compared to the costs of the programme.

Duration and practical arrangements: This component will be completed by the end of year 4.

Sub-study 4


Rapid Diagnostic Screening
Chest x-ray suggestive of active TB on the MXU and able to provide spot sputum sample
Randomised
Control arm
Standard Care
Accompanied same day referral to local TB clinic. Find & Treat advocate for sputum sample processed within 24 hours at local TB clinic.
Intervention arm - Cepheid Xpert®
Sputum PCR samples processed on the Mobile X-ray Unit
Sputum PCR POSITIVE
Sputum PCR Negative With
• Weight loss
• Night sweats
• haemoptysis
Sputum PCR Negative No symptoms
Community follow up by Find & Treat: Patient asked to produce two further sputum samples
Referral to TB Clinic
For clinical assessment which may include isolation and commencement of TB treatment
Patient asked to produce two further sputum samples
Any POSITIVE
All NEGATIVE
Patient offered a repeat chest x-ray on the MXU three months after the original Chest x-ray. Travel expenses will be covered for this
Outcomes follow-up by "TB Reach":
•Time to sputum smear result
•Number of clinical visits to diagnostic conclusion (smear, culture, PCR)
•Time to treatment on-set
•Loss to follow-up
•Hospitalisation
•Isolation

SUB-STUDY 5. Virtually Observed therapy (VOT) versus Directly Observed Therapy (DOT)

1. Primary objective:
   - To compare virtually observed therapy (VOT) arranged by the research team in conjunction with Find & Treat, a specialist community team using internet based technologies with standard directly observed therapy (DOT) arranged by a TB Service to support treatment adherence.

2. Secondary objectives: To determine the effect of intervention on:
   - Proportion of culture conversion
   - Proportion with treatment completion
   - Proportion loss to follow-up
   - Rates of hospitalisation.

Target population: All TB patients who are eligible for DOT.

Inclusion and exclusion criteria: Any patient 16 years of age or older eligible for DOT at participating clinics who is suitable for VOT.
Exclusion criteria – Patients who refuse DOT, those who refuse to participate in the study and those who are not suitable for VOT due to:

a) Significant concern that the participant will lose, sell or seriously damage the equipment or lack the ability to self-administer treatment under video observation
b) No secure storage to keep VOT equipment or private area to take medication
c) Insurmountable language or computer literacy barriers.

Most homeless people (with the exception of street homeless) are expected to be able to be included with appropriate support. Patients on DOT who are initially deemed unsuitable for VOT can be reconsidered if their circumstances change so that they meet the criteria. Similarly patients for whom VOT is not working will be returned to standard DOT.

Sub-study 5

Individual Randomisation	**Intervention Community-based VOT**	**Control Clinic-based DOT**
Setting	London TB clinics currently using a standardised risk assessment tool to identify patients likely to benefit from DOT.	
Frequency of DOT	According to schedule chosen by clinicians (this may be daily or thrice weekly.	
Baseline information	Collected by clinic specialist TB nurse • Risk factor for TB • Risk assessment • Identify patients eligible for DOT	
Initial activities	Clinic specialist TB nurse responsible for patient care • Provides verbal and written information about the study • Recruit and seek consent of eligible patients • Randomise patients into either the intervention versus control arm • Administer first DOT Research nurse - Provide telephone support as needed, including at the time of recruiting	
VOT vs DOT Provider	Research nurse: • Explain VOT study again	Clinic specialist TB nurse based at participating clinics.

	• Reassess patient suitability for VOT • Arrange onward care alongside Find&Treat i.e., - Provide VOT equipment (laptop with wireless data access), training and information - Support patients to attend regular clinic follow-up visits agreed by treating clinician.	
VOT Supervision	Research nurse will - Observe the patients take their treatment through a video link between patients home and study office using a laptop with secure internet connection. - Provide on-going support i.e., weekly "face-to-face" internet chats to review patients' status, clinically (e.g., side effects) and socially.	N/A
Routine information collected	By research nurse • Attendance • Doses taken • Side effects • Outcomes (diagnostic, treatment and clinical) • Loss to follow-up.	By clinic specialist TB nurse • Attendance • Doses taken • Side effects • Outcomes (diagnostic, treatment and clinical) • Loss to follow-up
Additional information collected	By research nurse • Quality of life questionnaire (EQ-5D) • History of hospitalisation • History of sleeping rough • History of imprisonment.	By clinic specialist TB nurse • Quality of life questionnaire (EQ-5D) • History of hospitalisation • History of sleeping rough • History of imprisonment.
Incentives	The study will not provide financial incentives to attend VOT or DOT. However, participants in the VOT are allowed to keep the computer at the end of the study: and the clinic arm will retain flexibility to use incentives as is current practice.	

Sample size: Aim to recruit 400 patients (200 into each arm).

Participant follow-up procedure: In both arms a sputum sample will be collected 2 months into the treatment, and specimen cultured by the local microbiology laboratory to identify culture conversion (absence of viable organisms in the sputum). Data will be transferred to HPA for linkage to identify those who developed drug resistant TB and relapse case within 24 months of treatment completion.

Economic evaluation: We will compare the costs of delivering DOT in the clinic vs community VOT from an NHS perspective. The mathematical model will calculate the number of cases averted (including drug resistant cases) through improved adherence.

Duration and practical arrangements: This study will be completed by the end of year 4.

SUB-STUDY 6. Cost effectiveness.

1. Primary objective:
   - To determine the public health impact and cost effectiveness of the different interventions in sub-study 1 – 5.

2. Secondary objective:
   - None

Setting: The model considers high-risk groups (homeless & prisoners) as well as the general population and will be generally applicable to TB control in low prevalence countries where TB is concentrated in hard-to-reach groups.

Target population: Homeless people, prisoners and general population at risk of TB in London.

Inclusion and exclusion criteria: Not applicable as this study relies on data analysis from sub-study 1-5.

Measurements: Most importantly, numbers of averted cases of infection, disease (improving health) and treatment (saving treatment costs) resulting from shortening (or preventing) the infectious period, and the most cost-effective combination of intervention elements in different settings. Other measures will include incidence and prevalence of latent infection. Changes over time will be reported as screening will initially increase numbers going on to treatment; subsequently, it will reduce them through averting infections. Benefits persisting in the decade beyond the end of the intervention will be calculated. Different intervention scenarios will be examined to determine the optimal strategy; sensitivity analysis will indicate the certainty of predictions.

Rates of progression in different groups are important epidemiologically, and having data on both the prevalence of latent infection and the prevalence of active disease in the same group will allow us to estimate them using the model.

Sample size: Aggregate data records from sub-study 1 - 5 will be used for this projected analysis.

Participant follow-up procedure: The model will be projected to 10 years beyond the end of the programme grant, i.e. 2023.

Economic evaluation: Output from the transmission model allows calculation of the cost per case treated and per case averted, taking into account reduced treatment costs through averting cases of infection and disease.

Duration and practical arrangements: Mathematical modelling expertise is required at the start to ensure that the study collects data suitable for model parameter estimation. Then attention will turn to theoretical development and programming of the model (in the language, C++), including debugging, testing and validation, so that it is ready to use the empirical data when they become available. The most intense effort will be in the final years of the project, when data are available for model fitting, sensitivity analysis and examination of multiple different intervention scenarios to optimise the public health impact of IGRA / MXU screening and treatment. Computational analysis will use the high-performance computing cluster at Imperial College.