Drug Resistant TB contacts electronic registry

Contact tracing in multi-drug resistant TB; a cohort study using a data toolkit that helps TB nurses contact trace systematically according to WHO and NICE guidelines, improving adherence to guidelines and patient outcomes

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Sponsor

For LSHTM sponsored studies:

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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This protocol describes the 'DR TB contacts Registry' study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

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GLOSSARY OF ABBREVIATIONS

MDR TB	Multi-drug resistant Tuberculosis
XDR TB	Extensively drug resistant tuberculosis
LTBI	Latent Tuberculosis infection
TB	Tuberculosis
WHO	World Health Organisation
NICE	National Institute for Clinical Excellence
UCLH	University College London Hospital
NHS	National Health Service
LSHTM	London School of Hygiene & Tropical Medicine
HRA	Health Research Authority
eCF	Electronic consent form
TMF	Trial master file
ISF	Investigator site file
DHIS2	District health information software 2
IVDU	Intravenous drug users

KEYWORDS

Multi drug Resistant Tuberculosis (MDR TB)
Contact tracing
Screening
Mobile application (app)
Registry
District Health Information Software2 (DHIS2)

STUDY SUMMARY

TITLE Drug Resistant TB contacts electronic registry.

DESIGN An observational cohort study of exposed close contacts of patients with MDR TB. Within this cohort is a nested feasibility study for a novel technology. In this feasibility study the technology – a software tool is assessed for use in enrolling participants into the systematic cohort study. Following contacts of persons with MDR TB from MDR TB treatment start of index MDR TB patients for 2 years.

AIMS

1. Systematically enrol all exposed close contacts of index cases of MDR TB at participating NHS MDR TB treatment centres into an electronic research registry to 2 years after presentation.
2. Pilot the use of a software tool to enter data into the registry enabling nurse led MDR TB contact tracing.
3. Provide rapid feedback of data to TB nurses enabling use of their data in clinical monitoring of MDR TB contacts.
4. Improve data collection and support adherence to national and international guidelines for exposed contacts of patients with MDR TB.
5. Explore stakeholder opinions on data sharing within a secure registry.
6. Assess software tool usability and uptake by TB nurses.
7. Assess software tool reach and fidelity.

OBJECTIVES

1. To develop the software tool (using open source DHIS2) to enable MDR TB contact tracing.
2. To systematically enrol MDR TB exposed contacts at participating clinical facilities into an electronic registry.
3. To beta-test in early-adopter sites and assess DHIS2 app feasibility and user acceptability
4. To deliver monthly automated registry updates to participating sites
5. To evaluate the impact of the MDR TB contact registry on contact surveillance (reach, and fidelity – for 2 years from registration)
6. To describe the epidemiology of active TB and latent TB infection (LTBI) in MDR-exposed contacts at 0, 6, 12, 18 and 24 months after exposure two years from diagnosis in routine settings.
7. Analyse loss to follow up of MDR TB contacts during a 2-year active monitoring period.

OUTCOME MEASURES The primary outcome measure in the observational cohort is to observe incident TB and LTBI in MDR TB close contacts at 2 years post MDR TB treatment start. A quantitative component will describe fidelity and uptake of the software tool used in data collection. This will be completed using total numbers of contacts entered into the registry compared with known MDR TB contact numbers from patient notes. A qualitative component will explore TB clinician attitudes and uptake of the software tool with pre and post deployment structured interviews. Anonymous questionnaires will assess stakeholder perceptions of personal data use in a registry and the proportion of eligible participants who engage with the study.

POPULATION All close contacts of MDR TB at NHS MDR TB treatment centres.

ELIGIBILITY Exposed close contacts with an index MDR TB patients registered at participating NHS MDR TB treatment centres. It captures those with intense contact through bed sharing, bedroom sharing, household sharing or daily contact with the index case.

Contacts of Drug susceptible TB will be excluded.

TREATMENT No treatment to be given outside of routine NHS care. This is an observational cohort study with a feasibility data collection study capturing clinico-epidemiological data on MDR TB contacts with routine tests for LTBI.

DURATION Duration is 2 years for all MDR TB contacts, the study will close once 80 index patients' contacts have been followed up for 2 years. We expect the database to continue once this study has closed.

1. INTRODUCTION

1.1 BACKGROUND

How big a problem is TB and MDR TB?

Despite global efforts tuberculosis (TB) is still an uncontrolled problem with an estimated 1.6 million deaths and 10 million people with TB in 2017; only 6.4 million of which were reported. It is the leading infectious cause of death worldwide, causing more mortality than HIV(1). This aerobic bacillus is mainly transmitted via aerosols. The complete mechanisms of its transmission, immune recognition of infection, clearance or persistence of infection and progression to active disease are not fully understood(2). In 2017 there were 558,000 estimated cases of multidrug resistant (MDR) and rifampicin resistant (RR) TB worldwide, of which only 25% were started on effective treatment (1). MDRTB is defined as TB resistant to at least rifampicin and isoniazid, requiring prolonged therapy, which has significant toxicities and a negative impact on quality of life (3). Treatment success rates for MDRTB are still only 55% globally. Often countries do not have access to the drugs required to treat MDR or XDR TB effectively.

In England in 2018 there were 47 cases of Rifampicin resistant and MDR TB and 4 cases of XDR TB (4) . This has been decreasing since a peak in 2011 of 88 cases (5). The majority of these cases are in London, in patients born elsewhere and within 5 years of arrival to the UK. A large burden of UK cases are in patients who were born in Eastern Europe or the Indian subcontinent(4). Close contacts of MDR TB have a higher risk than the general population to go on to develop TB (6) yet there is a lack of evidence around how to manage MDR TB exposed contacts(7).

Controlling spread:

Studies on exposure risk in TB contacts describe increased risk of developing TB disease or LTBI with increased hours spent with the index patient per day. Sharing a bed overnight or sharing a room overnight are reliably found to carry the greatest risk (8,9). TB spread is related to infectiousness of index case and duration of exposure (10,11). Risk factors for ongoing spread are pulmonary TB and smear positive cases (12). In low TB incidence countries alcohol excess, IVDU and homelessness increase risk of developing TB perhaps due to increased exposure. The highest rates of transmission are documented in households, schools and prisons (12). It is also clear that the risk for developing TB persists for up to 5 years after an index case of TB is treated but is at its highest for the following year (13). New technology in genomic epidemiology enables linkage of cases within households (14). This highlights the potential prevention in household clusters but does not prove the direction nor the origin of TB spread. Both a Cochrane review and systematic review highlight the high rates of active TB and latent TB infection(LTBI) in TB contacts in low, middle and high income countries (13,15). Rates of TB and LTBI are higher in TB contacts in low and middle income countries and in child contacts up to the age of 5 years(13). MDR TB is as transmissible in

household contacts as drug susceptible TB (16). MDR TB patients continue to produce smear positive sputum for longer than drug susceptible TB (6).

TB control programs in countries with high TB prevalence rely on passive case finding, which relies on patients seeking health care once symptomatic. There are many TB infected and TB symptomatic patients' not accessing health care for TB. Contact tracing has been suggested as a measure to control TB spread (10) and it is known that preventative treatment of LTBI for the third of the world's population with LTBI could stop the 10% of those that go on to develop active TB (WHO global report, Tuberculosis Fact sheet 104). Contact tracing and monitoring for MDR TB is a productive exercise and deserves further research in all incidence settings.

An evidence gap exists in low and middle income settings in casual TB contacts; prisons, homeless shelters, IVDU clinics, work places and childcare centres. In high income settings these are documented sites for ongoing transmission(13). It is also unclear if contact tracing in low income high prevalence countries is cost effective. In a Ugandan study, passive case finding coupled with household contact tracing was cost effective however active case finding plus passive case finding was not (17). In Ethiopia symptomatic contacts of MDR TB were screened in a feasibility pilot study, close contacts without active TB were followed up for 2 years(18), 1 in 10 family members in contact traced households had MDR TB. This study completed contact tracing in only a small proportion of the index MDR TB cases. Contacts with MDR TB frequently had a history of previous TB treatment, making it unclear who the true index case is or if community transmission rather than household transmission plays a bigger role than is understood. Either way there is clearly a place for contact tracing of household contacts in this high prevalence setting.

<u>What is known about LTBI:</u>

A 2013 systematic review of TB prevalence in contacts reported wide variation. In low and middle income settings 51.5% of household contacts had latent TB infection (13). Overall TB in household contacts was 3.1% and MDR or XDR TB rates were 3.4%. In high income settings, TB prevalence in contacts was 1.4% and latent infection prevalence was 28.1%(13). TB incidence in the first year after exposure to an index patient is 1478 cases/100000/year in low and middle income countries and 524 cases/100000/year in high income countries, a statistically significant difference. In the second year after exposure incidence falls to 831/100000/year and 152/100000/year. A subsequent spike in incidence occurs in the third year after exposure with 1101/100000/year and 233/100000/year before the incidence falls away(13). A previous systematic review in 2008 of low and middle income settings identified LTBI in over 50% of household contacts(19). Follow up duration following TB contact is well established to last 2 years (20). Conversion to a positive tuberculin test within this period is recognised as recent infection.

Diagnosis of latency is difficult in TB high endemic settings BCG usage has been extensive in most countries and cross reactions or false positives make interpretation of TST difficult. A negative test requires serial

TST follow ups, difficult in any resource poor setting. Availability of TST is low and Interferon gamma release assays (IGRA) even lower.

Transmission of MDR TB within the UK is low and identification of LTBI would impact on MDR TB rates (21). Systematic reviews of TB in high income countries identify reactivation of LTBI as the cause of the majority of TB cases. Unanswered questions remain regarding what to do with LTBI in MDR contacts. There is no proven treatment for LTBI in MDR strains. Some research suggests using drugs tailored according to drug susceptibility testing of the index case, however these drugs are often poorly tolerated and no evidence base currently exists (22). Importantly household matching of MDR TB contacts that go on to develop TB are discordant (6,23).

Guideline Advice

The WHO advise that 'systematic recording and reporting' systems should be developed to aid management of LTBI (7). There is an evidence base behind the WHO and NICE guideline for TB contact tracing in low prevalence settings and for select groups in high prevalence countries (children <5years and people living with human immunodeficiency virus (PLHIV) however it is limited (24). WHO recommend systematic screening in low incidence countries in household contacts, PLHIV and in silica exposed workers (24). WHO and NICE have well established guidelines for contact tracing and identification of LTBI in TB (25). Screening for LTBI should occur in all high risk contacts of infectious TB in low incidence countries. This is done with symptom screening, sputum analysis, tests to identify latent TB (Tuberculin skin test (TST) or interferon gamma release assay (IGRA)) and chest radiographs (CXR).

In MDR TB the guidance is less clear and what should be done with identified cases of LTBI exposed to MDR is as unclear (26). The WHO recognise a lack of available evidence on this subject and advise an individual risk assessment in patients with latent TB following contact with MDR TB (7). In high risk contacts with proven infection preventative therapy is now an option, though which drugs and for what duration is still unclear until three RCTs report. All other MDR TB contacts should be screened for symptoms and followed for 2 years (7). New cases of MDR TB need to be identified, isolated and treated. A systematic process must be developed and deployed to achieve this with a secure method of sharing case information to improve clinical service and facilitate research into how we control spread and manage LTBI (27). Treating patients with latent MDR TB without an evidence base could be harmful, drive resistance and expose patients to toxic side effects.

1.2 RATIONALE FOR CURRENT STUDY

MDR TB is an evolving threat the World Health Organisation (WHO) aims to eliminate as part of the 'End TB Strategy'. Aiming to eliminate MDR TB has many facets, one of which is prevention of spread through contact tracing. Identifying contacts of patients with MDR TB and screening them for active disease, latent

TB infection or high risk exposure is an essential element of controlling ongoing spread. Contact tracing is part of the WHO guidelines for high, middle and low TB prevalence countries. It is part of national guidelines in high income/low incidence countries but is not routine practice in low income/high incidence settings where its role is as yet unclear. Even in high income countries contact tracing is done at a local level by individual nurses; there are no information technology systems in place nor is there a co-ordinated response. Contact tracing data is collected by hand, kept by individual nurses with individual storage systems and not collated in a uniform manner. Public Health England (PHE) collects data on all cases of LTBI through a web portal (25) but does not collect data on TB exposed but currently uninfected contacts. Nor does this enable the full 2 year follow up advised. International guidelines have been formulated with a limited evidence base. In order to improve the existing evidence the current guidelines need to be used systematically before we can assess their effectiveness. This proposal to create a web based resource will allow development of several benefits: improvement of contact tracing for MDR TB, enhancement of TB control efforts and reduction of MDR TB spread. A software tool with web browser and mobile app interface (or software tool from here on) has been developed to help TB nurses follow guidelines and to establish a registry of exposed MDR TB contacts.

Our aim is to improve and systematise MDR TB contact tracing in England. Ensuring the WHO guidelines are followed for all close contacts of MDR TB and identifying what happens to contacts over the guideline two year follow up period. A systematised registry will provide significant operational research opportunities enhancing our understanding of the consequences of MDR TB exposure and whether these vary between settings. There are further key utilities to this resource; an existing electronic registry will be invaluable when a treatment for MDR LTBI becomes available, if further research into this is required a registry of eligible participants will streamline this process and the contacts will benefit from the new treatment.

To facilitate this software tool has been developed to be used on clinic computers and downloaded to android mobile devices. It allows systematic recording of contact screening questions that are routinely asked of close MDR TB contacts but usually collected on disparate hard copy paper records. This data is encrypted in both web browser and in the application on saving and will populate a database kept on the London School of Hygiene and Tropical Medicine (LSHTM) secure server. A summary dashboard will be generated providing TB nurses with summary information for each index case and their contacts. These will be visible through their access to the software web browser and emailed via an NHS account to the TB clinic's NHS email account aiding ongoing clinical care and local record keeping. This app will follow the NICE and WHO guidelines providing uniform assessments, aiding TB control efforts and patient care. The encrypted data with person identifiable information will be kept encrypted on the LSHTM secure server to be used as a research database. Patient identifiable location data is required to allow mapping of potential MDR TB spread. Data will be decrypted on download to a LSHTM computer with a decryption key.

This software tool will be piloted for the small number of MDR TB index patients and their patients in England following our initial pilot in Peru and interest from colleagues managing MDR TB patients within the NHS. We plan to restart the initial pilot in the North Central London TB clinic simultaneously. As previously stated this subsequent roll out to other NHS MDR TB centres requires further ethical review. This current study is an observational cohort study with a nested feasibility study for this data collection system. It needs to have international applicability and broad feasibility. Software tool uptake will be assessed with mixed methods including structured interviews and quantitative analysis of numbers of MDR TB contacts enrolled within the app compared with those documented in paper notes.

2. STUDY OBJECTIVES

Primary

To describe TB and LTBI incidence rates in exposed close contacts of MDR TB at 2 years after their exposure to MDR TB patients in an observational cohort study whilst entering them onto a contacts registry.
To use a software tool with web browser and mobile app to enter MDR TB close contacts onto this registry. This is to be used alongside existing NHS MDR TB contact screening services to improve data collection, assist adherence to international guidelines and provide a structured system for data collection.

Secondary

- Compare total numbers of contacts entered onto the registry with known index MDR TB patients and their contact numbers from patient notes.
- Assess TB nurses' uptake of the app with a structured interview questionnaire.
- Assess stakeholder (index patients and contacts) uptake and opinions on personal identifiable data held within a database through anonymous questionnaires.
- Analysis of Loss to follow up of MDR TB contacts during 2 year active monitoring period.

3. STUDY DESIGN

All MDR TB exposed close contacts at all NHS commissioned MDR TB treating centres will be approached to consent to this observational cohort study. A list of these centres is added to the appendices. They will be asked to consent to enrol in a cohort study where their personal identifiable data will be entered onto a registry using a LSHTM housed District Health information software 2 (DHIS2) software with web browser or mobile data app. This will be used by TB nurses to gather information on the index MDR TB cases and answers to screening questions asked of the index cases' contacts related to risk of exposure, symptoms, previous TB and latent TB infection (LTBI). The software tool will collect data on TB and LTBI diagnosis and the results of clinical screening tests. The contacts will be followed up 3-6 monthly for 2 years after diagnosis of the index MDR TB patient, following the WHO algorithm. The registry is expected to continue once this study terminates.

Within routine NHS care MDR TB contacts are screened at index patient diagnosis of infectious MDR TB. Screening includes identification of symptoms, clinical examination, sputum or other clinical samples are taken for microbiological analysis, chest radiograph and blood tests for LTBI; these include tuberculin skin tests (TST) and interferon gamma release assays (IGRA). This is repeated at 6 monthly intervals for 2 years after exposure to MDR TB. This study will not change this NICE guideline care but document it all uniformly in one place and collate the outcomes for all MDR TB contacts, something which is currently not done.

No study staff will be employed but current TB nurse specialists within the NHS will be supported to use the software tool through a training session run by the research team. Following this there will be ongoing clinical support for technical problems through the research team.

The mobile app is compatible with android devices only, the online tool can be accessed through any internet browser including Chrome, Firefox and Internet explorer. The software tool was developed in DHIS2 as a module nested alongside the WHO DHIS2 tool for TB case surveillance(28). Our software tool can be used in conjunction with or separately to the WHO module. Where the app is used spyware protection will be downloaded simultaneously to ensure the android has virus protection software installed.

The index case will be consented at the point of proven MDR TB diagnosis in TB clinic, the consent will be separate, and paper based. The consent form must be completed prior to data collection. The personal identifiable information kept in this form on the index case will be their unique NHS number, address, name, date of birth and email on consenting. The consent form and patient information sheet (PIS) will be given to the index case participant. The TB nurse can then enter participant answers into the software tool which captures what type of TB the index patient has, if they have had a cough, if their sputum is positive for acid and alcohol fast bacilli (AAFB), what drug resistance is present and how many exposed close contacts they have. Patients in the NHS routinely give verbal consent to this longstanding clinical practice. The tool does not aim in any way to change existing clinical practice. All personal identifiable and clinical data is entered, saved and encrypted during the patient consultation. The MDR TB contacts will be seen at a later date, as is routine practice, in their homes or in clinic by TB nurses. They will each be asked to provide consent for their personal data to be entered into the software tool database for clinical care and will be asked to consent to their personal data to be kept in a research database separately. The contacts will have personal identifiable data stored on the database, including their NHS number, name, date of birth, address, phone number and email address. Both the index and contact participants will be given or emailed a soft copy of their consent form and patient information sheet. Once the contact has been consented the TB nurse will be able to enter clinical data as per NICE and WHO guidelines. Again, all personal identifiable and clinical data is entered, saved and encrypted during the consultation.

The software tool used is DHIS2 housed on a secure server within LSHTM which allows secure password protected encrypted data entry. Once entered the anonymised data can be viewed on a dashboard and the participant individual data can be accessed by the clinic team assigned to them. Additionally, on completing the form and saving data, all the data is encrypted. It is then stored encrypted at all points; in the server and on download to a LSHTM computer. Due to encryption no data will be retrievable from the computer, tablet or database (e.g. in the event of loss, hacking or theft). On accessing the software tool, the user will be required to login and log out using a personal ID and password. Monthly reports will be emailed out to the TB clinic NHS email account via an NHS email account. These reports will contain a pdf file containing the results captured on the software tool of the MDR TB contacts review. An audit trail of end user activity will be kept. In the earlier ethically approved version of this protocol a mobile application was the preferred interface of the software tool, however for this amended protocol and subsequent roll out to all MDR TB treating centres the web browser interface is preferred.

Exposed close MDR TB contacts of consecutive index patients will be consecutively enrolled in this contact tracing study. Index patients will be microbiologically confirmed with MDR TB disease. Consecutive contacts will be enrolled and followed up 3-6 monthly for a period of 2 years, this will occur alongside current clinical practice. At 6 monthly follow up appointments in the NHS close contacts have repeat screening for TB and LTBI. The software tool will be used to capture whether the repeat screening has happened, what the outcome of the screening is and the next planned follow update.

This observational cohort study will run until all participants have been followed up for two years. However, the registry is expected to continue beyond the reach of this initial study. Any onset of TB disease or LTBI within this period will be captured via on the registry. Once the data is entered into the software tool it will be sent and stored on the 256bit encrypted DHIS2 LSHTM secure server with an information governance toolkit. The data will be sent back to TB clinicians at their NHS email in a pdf and an excel file to enable clinical care and ensure an audit trail. The clinician will be able to access participant data from their TB clinic only.

The aim is to collect data only, no medical interventions or treatment will be part of the study but clinical management will continue alongside the study as routine practice in the NHS according to international guidelines. We aim for it to be used alongside routine practice in NHS care. Documentation in patient notes will not be altered and the contact tracing excel and pdf reports generated can be kept in both hard and soft copy by the TB nurses.

Any participants identified with TB will be treated as per national and international guidelines. Participants identified as having LTBI will be treated as per national and international guidelines.
No treatment will be given outside of routine practice.

TB clinicians will be asked to complete a questionnaire prior to using the software tool. After enrolling 5 contacts or 3 index patients and their contacts 10 TB clinicians will be asked to complete a structured interview on usefulness, usability and uptake of the software tool. This has been expanded to allow clinicians in additional clinics input into the feasibility, utility and applicability of this tool.

Anonymous questionnaires will be given out to eligible participants alongside the PIS in the clinic waiting room. Questionnaires will explore stakeholder perspectives on personal data sharing in an encrypted registry. The questionnaire will capture the proportion of eligible participants who plan on consenting.

A total of 80 participant 'contacts' will be recruited. This cohort study was started in at the North Central London TB clinic but if mobile app uptake is successful it will be rolled out to further TB clinics across London. Due to TB clinic requests it will be opened up to MDR TB treating centres across England. These additional clinic locations are now included as amendments to LSHTM ethical review and for ethical review within the NHS Integrated Research System (IRAS).

3.1 STUDY OUTCOME MEASURES

This is an observational cohort study following up MDR TB close contacts for 2 years from exposure. The incidence rates of TB and LTBI in this group at 2 years will be described. Within the cohort a nested mixed methods study will be completed assessing the use of the software tool. Quantitative methods will be used to describe total numbers of contacts within the software tool against total numbers of contacts in index patient's paper notes. Concurrently TB clinician attitudes and uptake of the software tool will be explored with qualitative structured interviews. Anonymous stakeholder (index cases and their contacts) questionnaires will provide data on the proportion of all invited participants who decide to participate and stakeholder opinions around holding personal identifiable data within a database will be explored.

Successful uptake of the software tool will be assessed with a comparison of total contacts collected with a complete data set within the registry, compared with total numbers of known MDR TB patients in each clinic and their documented contact numbers from patient notes. Both the reach and fidelity of the software tool will be assessed through identifying the proportions of MDR TB contacts entered into the app and the proportions of follow up visits completed within the two year study period.

TB clinician engagement with the software tool and successful uptake of the registry will be assessed with qualitative measures. We will ask 10 TB clinicians entering patient data to consent to two 10 minute structured interviews, asking focused questions on usefulness and usability of the registry. It will contain open questions inviting feedback and encouraging constructive criticism, enabling the registry to develop in line with clinical need. Anonymous questionnaires will capture stakeholder perspectives on personal data collection within a registry and an assessment of the proportion of eligible stakeholders who join the study.

3.2 RISKS AND BENEFITS

The anticipated risks are around personal data security and information governance. This pertains to all locations at which the data is held: on the software tool prior to sending; on transmission to the secure server at LSHTM; on transmission of results from the LSHTM server to back to the TB clinicians and on downloading from the LSHTM server to a secure computer at LSHTM. To enable the application usage it will have to be downloaded on to provided android devices. The android device will have a security spyware app downloaded onto it.

In this amended protocol version access in extended MDR TB treatment clinics will be via web browsers. To access the software tool the server address is entered into the browser, an individual login and password combination allows access to view participant data at that location level only.
To download the mobile app a personal login and password is required and again each time the user enters data into the app. Once the data is entered the app asks you to save the data to the server. On agreeing to save and send, the data is encrypted. It is then kept in an encrypted form until it is downloaded to a secure computer at LSHTM. It will only be possible to de-encrypt the data with a secure RSA key.

The LSHTM secure server is secured with an Information Governance toolkit ensuring data security. The data will be downloaded encrypted onto a LSHTM computer only. The RSA key to de-crypt the data will be kept on a password protected secure external hard drive and one hard copy will be printed and kept in a locked safe at the LSHTM. Only the researchers involved in this study as listed in the protocol will have access to the key.
Participants will be consented according to General Data Protection Regulation (GDPR) legislation 2018 and the LSHTM Data protection policy.

The LSHTM secure server has an DHIS2 server established within it that is secure and maintained for this project alone. Storing data on the LSHTM server enables this project to function within a currently maintained system instead of requiring a separate DHIS2 server to be set up within each NHS Trust. This would require regular maintenance and support. This study will be rolled out to further TB clinics, only a central server will be able to collate the data from several sites into one database.

We will regularly check the security of data on the server, and through random checks on the downloaded mobile apps. This will be through regular audits of the data security.

The benefits include co-ordinating and structuring patient care in a systematic way. Capturing this data for future audit and service improvement. Enabling TB nurses work with an improved data collection process compared with the existing paper based system. Of particular benefit is the development of an information technology system enabling MDR TB control and reducing MDR TB spread. The research database will enable us to answer further research questions on this population. A registry of all MDR TB contacts will be invaluable in the event a therapy becomes available to clear LTBI. Participants will be easily accessed once a treatment or intervention becomes available for MDR LTBI.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 PRE-RANDOMISATION OR PRE-REGISTRATION EVALUATIONS

On microbiological diagnosis of an index case of MDR TB they are routinely asked for details of their exposed close contacts and permission for the TB nurses managing the index case to assess their close contacts for risk of TB infection spread.
The participants are close contacts of the index case and they require no tests prior to enrolment.

4.2 INCLUSION CRITERIA

All exposed close contacts of index patients with MDR TB in NHS MDR TB treating centres across England will be invited to enrol. To be a contact they must have been exposed to a case of MDR TB and judged to be close contacts according to the NHS and WHO guidelines on contact tracing. The participants are high risk contacts who co-habit or spend a significant proportion of their day with the index case.
It captures those with intense contact through bed sharing, bedroom sharing, household sharing or daily contact with the index case.

- All age groups included

4.3 EXCLUSION CRITERIA

- Contacts of Drug susceptible TB will be excluded
- Adults who lack capacity will be excluded

4.4 WITHDRAWAL CRITERIA

If the participant withdraws their consent for participation within the research registry they will be withdrawn from the study. Their data up to the point of withdrawal will continue to be held.

If the uptake of the software tool by TB nurses is unsuccessful due to user difficulties, organised retraining sessions for nurses will be run, and technical or clinical concerns will be addressed. However if the roll out of the software tool remains poor despite these measures the trial management group will consider stopping the study early.

7 SAFETY REPORTING

7.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant
Serious Adverse Event (SAE)	A serious event is any untoward medical occurrence that: Results in death Is life-threatening Requires inpatient hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability/incapacity Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

7.2 REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

7.2.1 Non serious AEs

A database of adverse events will be recorded. System users will be encouraged to report adverse events through a reporting system via NHS email. AE and SAE report forms will be made available to the TB nursing team during training and will be available via email. Each event will be individually investigated by the study team. Electronic reporting will allow an audit trail of all events and their investigation. All AE will be recorded in the participants' clinical notes.
The study team will provide continuous monitoring and support at the TB clinics. Any verbally reported AE at study visits will be recorded in the AE database by the study team. We will report a summary of AE on completion of the study.

7.2.2 Serious AEs

Serious Adverse Events (SAEs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information.

The only anticipated SAE will be breach of patient confidentiality or systems break down allowing access to patient identifiable information. This will be prevented as stated previously with password use and software tool encryption of data, password on download and on app opening prior to data entry, downloaded spyware for the android devices and IG toolkit on the LSHTM secure server. However if this does occur SAE reports will be sent to the supervising ethical bodies (both NHS and LSHTM) and a root cause analysis performed whilst further security measures are enacted. The individual study participants will be informed, a breakdown of the analysis given and further security measures explained.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

Contact details for reporting SAEs
Please send SAE forms to: DRTB.ContactsRegistry@nhs.net
Tel: 07739387816 (Mon to Fri 09.00 – 17.00)

8. ASSESSMENT AND FOLLOW-UP

Participants will be followed up every 3-6 months for 2 years as is currently recommended by NICE and WHO guidelines and routine practice at the NHS MDR TB treatment centres. Adults will be seen a total of 5 times as is routine in TB contact screening. In paediatrics appointments are every 3 months for the first year then six monthly thereafter. At each visit TB nurses ask routine screening questions for TB, these answers and test results will be entered into the software tool. The routinely asked data includes: whether the contact has symptoms of TB infection, if the contact requires a repeat chest radiograph, if repeat screening for LTBI has been completed and whether a sputum sample has been sent to the microbiology laboratory to look for TB. This data will be uploaded encrypted to the DHIS2 LSHTM server and patient follow up data will be emailed to TB clinicians in an updated in pdf and excel format.

8.1 LOSS TO FOLLOW-UP

Participants who are lost to follow up through non engagement with TB screening services or through clinical error will be recorded. Reason for loss to follow-up will be investigated. These data will be reported as part of the cohort study. Any participant who does not attend follow up will be contacted twice by the TB nurse as is routine practice, informing them of the need to attend TB contact tracing follow up.

9. STATISTICS AND DATA ANALYSIS

We will recruit 80 participant 'contacts' in London in an observational cohort study. These consecutively enrolled participants will be analysed after 2 years.

This is a feasibility study, no power calculation has been done. There are on average 50 MDR TB patients in England each year. Each MDR TB patient has 4-5 contacts. 10 TB clinicians will be asked to complete a structured interview, themes brought out in this will be discussed. The number of TB nurses to be interviewed has been increased to allow for increased coverage of feedback and participation in the roll out to further NHS sites and to improve the validity of the results.

We plan to analyse

- Incidence rates of TB and LTBI after 2 years of follow up in MDR TB close contacts.
- Engagement and uptake of the DR contacts registry app by TB clinicians through direct comparison of known numbers of index MDR patients and their contacts (found in paper notes) with the number of participants captured within the registry.

- Assess clinical usefulness through qualitative analysis of structured interviews.
- Proportion of eligible participants who consent to enrol in the study
- Acceptability of the software tool and registry amongst stakeholders.
- Describe how well MDR TB contacts are screened in practice and compare this with international guidelines
- Assess loss to follow up of MDR TB contacts and explore reasons for this.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. This covers the period required by both LSHTM and the NHS for data storage and archiving.

10. MONITORING

10.1 RISK ASSESSMENT

The study has no clinical intervention and is considered low risk.

10.2 MONITORING AT STUDY COORDINATION CENTRE

Data entered via the software tool will be uploaded to the server. Any data altered on the server will be monitored with an audit trail. Data can be updated via the app with subsequent forms and the participants' data added to on subsequent study visits. The TB nurses can verify the data they enter via the pdf and excel report but not alter the pdf. TB nurses will receive an excel chart for their ongoing clinical use. There will be no double data entry. If errors are made and recognised via the pdf report, the TB nurse will need to re-enter the data via the app. The software tool will have essential fields with pre-specified acceptable answers that must be completed before moving on to subsequent questions. This will reduce chance for missing data or inconsistent/unusual data.
The study site and NHS nurses will be trained by the research team to use the software tool. Follow up visits to monitor progress and app use will occur every two months. Two months after the study has started the TB nurses will be asked to complete a qualitative questionnaire on tool usefulness, usability and uptake.

10.3 MONITORING AT LOCAL SITE

TB clinics will be visited once/month to ensure concerns are addressed and software tool. uptake is continued. The LSHTM database will be monitored weekly for data integrity. The server will be monitored weekly for data integrity and the SAE/AE database will be reviewed weekly.

11. REGULATORY ISSUES

11.1 CTA (APPLICABLE IF A DRUG TRIAL)

11.2 ETHICS APPROVAL

The Study Coordination Centre will obtain approval from the LSHTM Research Ethics Committee, as well as the NHS Health Research Authority (HRA) for the study protocol, consent forms and patient information sheets. Local ethical approval from the Research and Development team at the Whittington Hospital will be sought. Throughout the study there will be repeated ethical review for any protocol updates.
All ethical applications and amendments will be stored in an investigator site file (ISF) and trial management folder (TMF). Annual progress reports to the ethical and regulation bodies will be kept in the (ISF/TMF). If substantial amendments are required the trial management committee will await ethical approval prior to implementation.

11.3 CONSENT

Informed consent will be obtained prior to the participant enrolling in the study or any data entered into the mobile data app specifically for the purposes of the study.

Consent to enter the study will be sought from each index and contact participant only after a full explanation has been given, a patient information sheet (PIS) offered and time allowed for consideration. Signed electronic participant consent will be obtained. The participants will receive a soft copy of their signed consent forms and PIS via email. The app will include as its first page an electronic consent page, on which participants will be invited to agree to consent for a clinical and a research database, enter the date and sign if they consent. Participants' GPs will be informed of their participation and participants will be made aware of this.
Parents and guardians will be asked to consent for their children to join the clinical and research databases. Children over the age of 10 years will be asked to give their assent to joining the study.
The TB nurses will be invited to consent to a structured interview by a study investigator.
All NHS staff involved in the study and inpatient recruitment will be provided access to good clinical practice teaching via online sources. This will be consolidated during a teaching session with the study investigator.

The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

11.4 CONFIDENTIALITY

Any participants' identifiable data collected by the Study Coordination Centre will be stored securely and their confidentiality protected in accordance with the GDPR Act 2018.

The software tool requires a login and password to download, it will require a login and password each time data is entered into a form. Users are forced to log out on exiting the tool. On saving the data it is encrypted. Spyware protection on the mobile device will protect against corruption of the data or access by a third party. It is then saved in an encrypted form at all sights going forward until a RSA key is used to de-crypt the data once on a LSHTM computer. The encrypted data will be transferred through a secure upload to the secure server at the LSTHM which is IG toolkit protected. The data on the server will be accessible only to the research study team as listed in the protocol. The research team will have administrator access to the DHIS2 LSHTM server. Administrator access to the DHIS2 server on the LSHTM server is password protected. The research team will be able to download the encrypted data to a password protected LSHTM computer. The LSHTM server will be audit trailed and backed up.

Once the data is decrypted a summary pdf will be generated for each TB clinic once/week. These files will be sent to the TB clinic NHS email address from an NHS email address. The end user in MDR TB clinic will be able to access a real time dashboard with anonymised summary data. TB clinic staff will only be able to access personal non anonymised data from patients within their NHS trust.

11.5 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.6 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.7 FUNDING

The Hospital for Tropical Diseases special trustees funded this study with a £3500 grant. Patients will not be given payments for inclusion in this study.
The initial budget is £3500, this includes purchase of an android mobile device for the TB clinic, travel to NHS trust sites, training sessions and stationary costs. The software tool and use of the secure LSHTM server are free. There will be no staff to pay. Further funding applications will go towards extension of the study at multiple sites and development of a mobile app to use on iOS devices.

11.8 AUDITS AND INSPECTIONS

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to Good Clinical Practice.

12. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

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APPENDICES

- PIS, Consent form, Assent form, Nurses PIS, Nurses consent form
- MDR TB software tool questions
- Structured pre and post questionnaire for TB nurse feedback
- Anonymous questionnaire for stakeholder feedback
- List of NHS commissioned MDR TB treatment centres
- GP letter
- LSHTM insurance form