Localised mobile active case finding with Truenat molecular testing for the effective diagnosis of tuberculosis (LOCATE-TB) Protocol

Protocol version 1.1

2022-08-03

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We, the undersigned, have reviewed and approved this Protocol, including Appendices. We will supervise and coordinate the clinical trial as described and ensure adherence to GCP/GCLP, the principles outlined in the Declaration of Helsinki and applicable regulatory requirements.

Name:
Institution:

Signature: _____ Date:_____

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Name:

Institution:

Signature: _____ Date:_____

Statement of Principal Investigator

The study will be conducted in accordance with ICH GCP Guidelines, to the extent possible in the research setting.

In signing this page, I, the undersigned, agree to conduct the trial in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me.

I will ensure that the requirements relating to obtaining Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review and approval are met. I will promptly report to the IRB/IEC any and all changes in the research activities covered by this protocol.

I have sufficient time to properly conduct and complete the trial within the agreed trial period and I have adequate resources (staff and facilities) for the foreseen duration of the trial.

I am responsible for supervising any individual or party to whom I delegate trial related duties and functions conducted at the trial site. Further, I will ensure this individual or party is qualified to perform those trial-related duties and functions.

I certify that Individuals involved with the conduct of this trial have completed GCP training within the past 3 years.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subject's names or personal identifying information may be disclosed. All subject data will be anonymized and identified by assigned numbers on all Case Report Forms, laboratory samples and source documents. Monitoring, auditing and inspection by the study sponsor and appropriate regulatory authority(ies), will be permitted.

Name of Principal Investigator: ___Rina Triasih_____

(Print)

Signature: _____ Date: _____

DD/MMM/YYYY

Protocol History/Amendment Summary

Protocol Version	**Date**	**Description of changes**	**Brief rationale**
Version 1.0 (Original Protocol)	2022-07-25	NA	NA

Abbreviations and Acronyms

ACF	Active case finding
AE	Adverse event
API	Application programming interface
CAD	Computer-assisted detection
CRF	Case report form
CXR	Chest X-Ray
DFAT	Department of Foreign Affairs and Trade, Government of Australia
DNA	Deoxyribonucleic acid
DR-TB	Drug resistant TB
DST	Drug susceptibility testing / Drug sensitivity testing
GCLP	Good clinical laboratory practice
GCP	Good clinical practice
HCW	Healthcare worker
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent ethics committee
IRB	Institutional review board
IT	Information technology
MDR-TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
MTBC	Mycobacterium tuberculosis complex
PCR	Polymerase chain reaction
PI	Principal investigator
PICF	Participant information and consent form
POC	Point of care
PRIME-TB	Papua New Guinea and Republic of Indonesia for Micro-elimination of TB, an Australian department of foreign affairs and trade (DFAT) Centre for Health Security funded project
RIF	Rifampicin
SAE	Serious adverse event
SAP	Statistical analysis plan
SIM	Subscriber identity module
SMS	Short message service
SOC	Standard of care
SOP	Standard operating procedure
TB	Tuberculosis
UGM	Universitas Gadjah Mada
USD	United States dollar
WHO	World Health Organization
WIFI	Wireless technology
ZTBI YY	Zero TB Initiative Yogyakarta

1 Research Outline

Title	Localised mobile active case finding with Truenat molecular testing for the effective diagnosis of tuberculosis (LOCATE-TB)
Protocol version and date	Protocol version 1 (2022-06-28)
Primary objective(s)	Assess the operational feasibility and acceptability of use of Truenat MTB Plus and MTB-RIF Dx testing on the Molbio Truenat platform within a mobile TB active case finding service in Yogyakarta, Indonesia
Secondary objective(s)	Within a community mobile active TB case finding service: 1. For bacteriologically confirmed tuberculosis cases, *compare* time to result for individuals diagnosed using decentralised Truenat MTB plus and MTB-RIF Dx against time to result for individuals diagnosed using centralised geneXpert testing 2. *Compare* the time to treatment commencement for decentralised Truenat MTB Plus and MTB-RIF Dx to centralised Xpert testing
Primary endpoints (outcomes)	1. The operational feasibility of point-of-care Truenat MTB Plus and MTB-RIF Dx will be assessed by: a. Adequacy of Truenat MTB Plus and MTB-RIF Dx training as measured by post-training assessment b. Operational performance of Truenat MTB Plus and MTB-RIF Dx as measured by platform failure rates and error rates c. Instrument user and health service provider views regarding feasibility and acceptability of Truenat MTB Plus and MTB-RIF Dx performed within a mobile active TB case finding service d. Screening participant views regarding acceptability of point-of-care Truenat MTB Plus performed within mobile active TB case finding service
Secondary endpoints (outcomes)	2. Reduction in time to result for those tested with Truenat MTB Plus and MTB-RIF Dx 3. For those with positive result on Truenat MTB Plus or GeneXpert (standard of care) the median time from initial assessment to TB treatment initiation

Trial design	This is a prospective mixed methods implementation science study to evaluate the use of decentralised Truenat MTB Plus and MTB-RIF Dx within a mobile active TB case finding service. For the primary endpoints the design for each component will be: 1a – application of a performance test to assess laboratory staff performance of trainees immediately after initial training 1b – Platform failure and error rates calculated from platform logs 1c – Survey of laboratory staff and health care workers on acceptability and operational challenges of decentralised Truenat MTB Plus and MTB-RIF Dx testing 1d – In-depth qualitative interviews of screening participants using purposive sampling to include a diversity of sex, age, whether tested microbiological positive or negative; and among contacts of known TB cases and community participants. For the secondary endpoints a randomised of decentralised microbiological testing using Truenat MTB Plus and MTB-RIF Dx (Truenat arm) compared with centralised GeneXpert testing (standard of care arm) will be conducted. Screening days will be randomised 1:1 to Truenat or standard of care.
Trial sites / setting	Indonesia has an estimated TB incidence of 301 per 100,000 population. The TB treatment coverage (notified/estimated incidence) in 2020 was 47%, with 52% of diagnosed cases bacteriologically confirmed. The Zero TB Initiative, Yogyakarta (ZTBI YY), is a partnership between Universitas Gadjah Mada, the TB program Yogyakarta, TB stakeholders in Yogyakarta and the Burnet Institute Melbourne. ZTBI YY includes a mobile community based active TB case finding service within Kulon Progo Regency (estimated 2021 population of 442 382), Yogyakarta City (estimated 2021 population of 415 382) in Yogyakarta, Indonesia, and Sleman Regency (estimated 2021 population of 1 087 339). The service which commenced in 2020, consists of a mobile van chest X-ray (CXR) based TB screening program covering all districts in these 2 sites. Potential 'hotspot' sites for screening are identified based on TB program records of previously reported TB cases within the preceding 3 years. Designated sites for screening are identified more than 2 weeks in advance to allow time to notify relevant authorities and the community near the intended screening site of the service and the free access to screening for TB. Community mobilisation is conducted by trained community cadres in collaboration with local community leaders and in consultation with the Dinas Kesehatan. Screening consists of symptom screening and CXR with computer aided diagnosis (CAD) software reading of CXR using the qXR (QURE.ai, Mumbai, India). Those identified as a screen positive, either with reported symptoms on symptom screen or positive CXR on qXR, have 1 spot

	sputum collected for molecular testing (currently at centralised laboratories on the GeneXpert platform with Xpert MTB/RIF cartridges). Household contacts of notified TB cases are screened for symptoms, undergo tuberculin skin testing and are referred for CXR at mobile screening or at the nearest CXR facility. Those screening positive on symptoms or CXR are asked to provide a spot sputum sample for molecular testing.
Trial population	The trial population includes different groups for different objectives and endpoints: • Laboratory staff and heath care workers trained to perform Truenat Mtb Plus and MTB-RIF Dx (1a) • Healthcare workers and laboratory staff involved in the use of Truenat Mtb Plus and MTB-RIF Dx (1c) • Screening participants (1d, 2, 3) The trial population for objectives 2 and 3 consists of participants attending case finding services in Sleman District and Yogyakarta City in Yogyakarta Province who screen positive for TB. These participants will consist of residents of identified hotspot screening areas, and household contacts of microbiologically confirmed index TB cases.
Sample Size	<u>Operational Feasibility and Acceptability</u> 1. Post-Training Assessment: All laboratory staff and health care workers trained in performance of Truenat MTB Plus (2 laboratory staff and 8–10 non laboratory staff) 2. Feasibility and HCW acceptability: Survey of all health care workers involved in the mobile screening service (10-15 HCWs including nurses, doctors and program staff) 3. Screening participant acceptability: purposive sampling representative of age groups, sex, bacteriological positivity and indication for screening (community screening or contact investigation) with 18-24 participants <u>Randomised Comparison (secondary endpoint 2)</u> The mobile service screens 1000 people per month with 12.1% of participants in rural areas screening positive and requiring microbiological examination of sputum samples. We will enrol participants for a minimum of 6 months and a maximum of 9. Which would result in between 3000–4500 persons screened in each arm (Truenat arm or standard of care centralised GeneXpert arm). Consequently, per the calculations below, the sample will be sufficiently powered to detect a difference in median time to result of one or more days with an alpha of 0.05 and power of 0.8. This would require a minimum

<table>
<tr><td></td><td>of 211 microbiological examinations in each arm. Throughput in of 3000–4500 persons would be expected to result in 363–544 microbiological examinations in each arm.

<table>
<tr><th>Median time to result standard of care</th><th>Median time to result Truenat</th><th>Alpha</th><th>Power</th><th>Sample size per arm</th></tr>
<tr><td>3 (sd = 14)</td><td>1 (sd = 14)</td><td>0.05</td><td>0.8</td><td>29</td></tr>
<tr><td>3 (sd = 21)</td><td>1 (sd = 21)</td><td>0.05</td><td>0.8</td><td>34</td></tr>
<tr><td>3 (sd = 14)</td><td>2 (sd = 14)</td><td>0.05</td><td>0.8</td><td>175</td></tr>
<tr><td>3 (sd = 21)</td><td>2 (sd = 21)</td><td>0.05</td><td>0.8</td><td>211</td></tr>
</table></td></tr>
<tr><td>Eligibility criteria for randomised comparison</td><td><u>Inclusion Criteria:</u>
• People aged 12 years old or above presenting to mobile CXR based screening in Sleman district and Yogyakarta City
• Able and willing to consent. For adolescents aged 12-17, verbal consent as well as parental/guardian informed consent will be required

<u>Exclusion criteria:</u>
• Cannot provide sputum
• Currently receiving anti-TB therapy
• Patients who are seriously ill and need to be admitted to hospital
• Patients with potential COVID-19 referred for further assessment</td></tr>
<tr><td>Eligibility Criteria operational feasibility and acceptability assessments</td><td>1. Post-Training Assessment (Objective 1a): All laboratory staff and health care workers trained in performance of Truenat assays who consent to participate
2. Feasibility and HCW acceptability (Objective 1c): All HCW involved in the mobile screening service who consent to participate.
3. Screening participant acceptability (Objective 1d): Adults 18 years of age or older who screened positive for presumptive TB in the active case finding program within the preceding 1 week and provide informed consent; and parents and</td></tr>
</table>

	legal guardians who have a child aged 12 to 17 years that screened positive for presumptive TB in the active case finding program within the preceding 1 week and provide informed consent.
Study Timeline	Ethics Clearance Q3 2022 Importation Q3 2022 Training + post training Assessment Q4 2022 Participant enrolment Q4 2022–Q2 2023 Data Cleaning + analysis Q3 2023 **Total duration** 12 months

2 Study Schedule of Events

Procedure	**Day 1**	**Day 1-3**	**Day 7-21**
Informed consent	x		
Eligibility assessment	x		
Enrolment	x		
Contact information	x		
Medical history + screening assessment	x		
TB diagnosis assessment	x		x
Referral to health facility for treatment based on Truenat MTB Plus and MTB-RIF Dx result		x	
Collection of data from health facilities and laboratory			x
Interview with selected participants for user acceptability			x

3 Introduction

3.1 Background

In 2020, an estimated 8.4% of the world's 10 million TB cases occurred in Indonesia, making it the country with the third highest number of cases globally. (World Health Organization, 2021)

The country is a WHO high-burden country for TB, multidrug-resistant TB and TB/HIV. (World Health Organization, 2021) Yogyakarta province, located in central Java, Indonesia's most populated island, notified 3 802 cases in 2018 for an estimated case detection rate of 34.2%. Against the background of COVID-19 disruption in 2021 this fell to 2 963 notified cases and an estimated case detection rate of 32%. There are multiple challenges to improving case detection in Yogyakarta including limited active case finding (ACF) among high-risk populations for TB, high proportion of people with symptoms suggestive of TB do not seek care or do not get tested, and a low coverage of GeneXpert testing for TB.

The Zero TB Yogyakarta Initiative commenced community active TB case finding in 2020 with a pilot in 2 sub-districts in the province. The Zero TB Initiative Yogyakarta is a collaboration between the Universitas Gadjah Mada, the Burnet Institute (Melbourne), the Yogyakarta TB program and local partners and stakeholders. In 2021, Zero TB Initiative Yogyakarta commenced scaling up active case finding to 2 regencies (Kulon Progo and Yogyakarta City) funded by the PRIME-TB project (Papua New Guinea and Republic of Indonesia for Micro-elimination of TB, an Australian department of foreign affairs and trade (DFAT) Centre for Health Security funded project). Kulon Progo is predominantly a rural context with a population of 442 382. From August 2022, case finding in Sleman District will be commenced and active case finding in Kulon Progo will be scaled down.

3.2 Current Active Case Finding (Standard of Care)

Active TB case finding is community-based and utilises mobile chest X-ray units deployed in vans. Screening sites are chosen based on identification of potential 'hotspots' through mapping of reported cases over the past 3 years. Prior to a mobile screening event, the local health authorities and community leaders are consulted and information is disseminated to the community to invite those living close in potential 'hotspots' to attend a free TB screening, with information given of what is provided and where to attend. The mobile van teams conduct screening with COVID-19 safe precautions and can screen 80-120 people per day. Each person attending is screened using a symptom checklist to check for: cough for more than 2 weeks; fever; night sweats; weight loss/failure to thrive; and haemoptysis. In addition, all persons over the age of 5 receive a chest Xray (CXR) on the van. The CXR is read by qXR, a computer aided detection software. Persons may screen positive based on either their reported symptoms or their CXR, which are suggestive of TB. Spot sputum sample collection is attempted from all individuals who screen positive. Samples are then transported as a batch to a central laboratory for GeneXpert testing.

Additionally, active case finding services include screening of household contacts. Newly registered TB cases are visited, and household members are screened for symptoms; for latent TB infection with a tuberculin skin test if eligible; and referred for a CXR at the mobile van services or nearest CXR facility.

Referral of sputum specimens centrally leads to delays in diagnosis and required extra visits from healthcare workers to follow up and contact patients with TB. Provision of TB molecular testing capacity within the mobile screening service could reduce diagnostic delays, reduce diagnostic loss to follow up and increase community acceptability.

3.3 Molbio Truenat Mtb Plus and MTB-RIF Dx

Molbio Truenat MTB Plus and MTB-RIF Dx (Truenat) are chip-based point-of-care rapid molecular assays for the detection of tuberculosis. The Truenat MTB Plus assay uses two devices — the first to extract and purify DNA (Trueprep Auto v2 Universal Cartridge-based Sample Prep Device) and the second (Truelab Real Time micro PCR Analyzer) to conduct PCR analysis to report a semi-quantitative result for MTBC. A positive sample can be loaded onto an additional chip (MTB-RIF Dx) for detection of rifampicin resistance. The Truelab Micro PCR Analyzer is portable, battery-powered and can provide a result in an hour. FIND's "real-world" multicentre diagnostic accuracy study has reported that "Truenat MTB, MTB Plus and MTB-RIF Dx assays have similar accuracy to Xpert MTB/RIF and can be performed at the primary healthcare centre level". (Penn-Nicholson, et al., 2021)

The Truenat MTB Plus and MTB-RIF Dx assays are WHO-endorsed with recommendations for use in adults and children with signs and symptoms of pulmonary TB. In the real-world multicentre study Truenat was reported as having a pooled sensitivity of 80% (75–84) and 96% (95–97) specificity when performed at primary health centres. (Penn-Nicholson, et al., 2021) In a comparison from sites where Truenat assays were conducted in parallel with GeneXpert MTB/RIF on the same specimens the authors reported no significant difference irrespective of smear status. (Penn-Nicholson, et al., 2021)

TRUENAT DEVICE COMBINATIONS AND SAMPLE THROUGHPUT

Devices	Throughput per 8-hour shift with optimized work flow[3]	Estimated throughput with "real-world" conditions
1 Trueprep Device + 1 Truelab Analyzer Uno	10-12 specimens	7-9 specimens
1 Trueprep Device + 1 Truelab Analyzer Duo	20-24 specimens	15-18 specimens
2 Trueprep Devices + 1 Truelab Analyzer Quattro	40-48 specimens	30-36 specimens

The Truenat PCR Analyzer is able to transfer data wirelessly in real time using a SIM card, WIFI or Bluetooth. Results can be sent by SMS or email to clinicians as well as to electronic patient and lab information systems (via a customised API), or through extraction of the data in text delimited format. The analyser can store up to 20 000 results in internal memory

Chips (at temperatures between 2ºC and 30ºC) and the sample preparation reagents (at temperatures between 2ºC and 40ºC) have a shelf-life of 2 years. The chips can be stored for up to 6 months at temperatures between 30ºC and 40ºC.

No air intake is required for the devices and they are therefore dust-resistant, although a dust-free operating environment is still recommended and the devices should be situated away from sources of electromagnetic interference and vibrations. They are quoted as being able to operate in relative humidity ranging between 10% and 80%.[1]

The in-built battery is cited as allowing for testing without power for up to 8 hours with battery-life specified as 5 years. Time to charge the analyser is quoted as 4 hours and 9 to 10 hours for the Trueprep device.

The portability and characteristics of Truenat MTB Plus and MTB-RIF Dx have the potential to enable point of care testing for TB, which could support TB diagnosis within primary health care services and within active case finding. This has the potential to reduce diagnostic delays and pre-treatment loss to follow up. However, the process for running the assay does rely on having trained, dedicated and skilled technicians.

4 Research Objectives

4.1 Primary objective(s)

1. Assess the operational feasibility and acceptability of use of Truenat MTB Plus and MTB-RIF Dx (Truenat) within community TB case finding service in rural Yogyakarta, Indonesia

[1] https://stoptb.org/assets/documents/resources/publications/sd/Truenat_Implementation_Guide.pdf

4.2 Secondary objectives

2. Comparison of decentralised Truenat to centralised Xpert testing within community mobile TB case finding service for median time to result for those tested
3. Comparison of decentralised Truenat versus centralised Xpert testing for median time to commence treatment for bacteriologically confirmed TB cases

5 Methodology

5.1 Study Design

This is a prospective mixed-methods implementation science study to evaluate the use of Truenat MTB Plus and MTB-RIF Dx (Truenat) within a mobile active case finding service. Specific methods will be used for each of the endpoints under the primary objective.

For the **primary objective**, operational performance will be assessed through laboratory staff and health care worker Truenat proficiency assessments after initial training (1a), and measurement of platform error rates during the study (1b). Views on the acceptability and operational challenges of Truenat will be assessed by a survey of laboratory staff and health care workers (HCW) within the program (1c). Individual in-depth qualitative interviews will be conducted with a purposive sample of screening participants to obtain their views on the acceptability and suitability of decentralised testing using Truenat (1d). The purposive sampling of screening participants will deliberately target the inclusion of participants representing a diversity of sex, age, microbiological positivity, and risk populations.

For the **secondary objectives**, a randomised comparison of decentralised microbiological testing using Truenat Mtb Plus and MTB-RIF Dx compared with standard of care centralised GeneXpert testing will be conducted. Screening days will be randomised 1:1 to the Truenat or standard of care, and the participants screened on those days then being assigned to corresponding study arm (Truenat arm or standard of care arm). Randomisation will be done across screening days within 2-week blocks for case finding activities. Only management staff will be informed in advance of the assignment for screening days to organise staff schedules. Community mobilisation will be done by the community cadre who will not know which screening type is being performed on any specific day, to reduce the potential for people in the community preferentially choosing a screening day based on which test will be available.

5.2 Participants

5.2.1 Primary objectives

The participants in the post-training proficiency assessments (objective 1a) will include laboratory staff and health care workers who have been trained to perform assays using the Truenat.

For the survey on acceptability and feasibility (objective 1c) all health workers and laboratory staff involved in screening and testing using Truenat will be invited to complete the survey.

For the qualitative interviews on Truenat acceptability for individuals being screened (objective 1d), participants will be individuals who have been screened using the Truenat strategy no more than 1 week prior to the interview. Individuals will be purposively sampled to capture perspectives of people residing in different areas; with different characteristics (age, gender); and with different results (positive and negative test results). To include perspectives relevant to the use of the Truenat strategy for children we will interview the parents or guardians of children.

5.2.2 Secondary objectives

For the secondary objectives the participants will include all people presenting to ZTBI YY community TB case finding services in Sleman district and Yogyakarta City who screen positive for TB.

Inclusion Criteria:

- Adults and adolescents 12 years old and above (including pregnant women)
- Able and willing to consent. For adolescents aged 12-17, verbal consent as well as parental/guardian informed consent will be required

Exclusion criteria:

- Unable to provide sputum
- Currently receiving anti-TB therapy
- Patients who are seriously ill and need to be admitted to hospital
- Patients with potential COVID-19 referred for further assessment

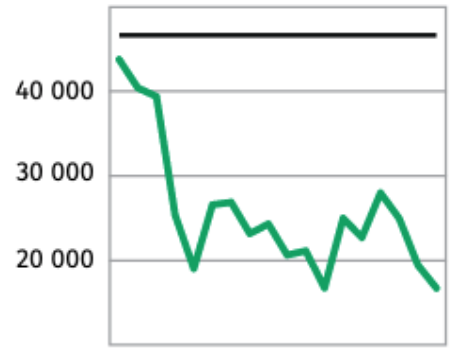
5.3 Study Setting

The settings for study are Sleman district and Yogyakarta City in Yogyakarta province in Central Java, Indonesia. Sleman district includes peri-urban and rural areas and has a total population of 1 087 339. Yogyakarta City includes urban areas and has a total population of 415 382.

In 2018, Yogyakarta Province notified 3 802 cases which equated to an estimated case detection rate of only 34.2%. Prior to the commencement of the ZTBI YY active case finding activities in the province were limited and not conducted routinely. In addition, there was very limited coverage of TB preventive therapy for latent TB infection, even among populations for whom it was indicated in national guidelines (people living with HIV, household contacts, children under the age of 5). Additionally, there was low coverage of testing with rapid molecular diagnostic tests among people with presumptive TB.

The onset of the COVID-19 pandemic in Indonesia is expected to have negatively impacted case finding for TB. In Yogyakarta City and Kulon Progo, routine TB program data has shown decreased notifications since Q2 of 2020 relative to the preceding years. Nationally, data in the 2021 Global TB Report indicates a marked decrease in case notifications from Jan 2020–June 2021.

INDONESIA CASE NOTIFICATIONS JANUARY 2020–JUNE 2021 (WORLD HEALTH ORGANIZATION, 2021)



Active case finding is therefore an important strategy to reduce the case detection gap and, potentially, to counteract the reduction in case notifications that has occurred as a result of COVID-19.

The Zero TB Initiative Yogyakarta (ZTBI YY) includes a mobile community based active TB case finding service within Kulon Progo Regency and Yogyakarta City in Yogyakarta, Indonesia. The service consists of a mobile van chest X-ray (CXR) based screening program. Potential

'hotspot' sites for screening are identified based on TB program records of previously reported TB cases within the preceding 3 years. Designated sites for screening are identified more than 2 weeks in advance to allow time to notify relevant authorities and the community near the intended screening site of the service and the free access to screening for TB, with community mobilisation by trained community cadres in consultation with the Dinas Kesehatan. Screening consists of symptom screening and CXR with computer aided diagnosis (CAD) software reading of CXR using qXR software. Those who screen positive based on symptoms or abnormal CXR (qXR interpretation) during screening have a spot sputum collected for molecular testing.

Household contacts of microbiologically confirmed cases are screened for symptoms and with tuberculin skin testing and also referred for CXR by mobile screening or at the nearest CXR facility. Household contacts who screen positive based on symptoms or CXR will have a spot sputum sample collected for molecular testing.

5.4 Study Procedures

5.4.1 Objective 1

1a. Adequacy of Truenat training as measured by post-training assessment

Laboratory staff from UGM with experience in performance of rapid molecular diagnostic testing for TB will be identified and trained as an onsite trainer and observer and certified by Molbio staff for this purpose. A total of 8 non-laboratory staff as well as 2 laboratory staff will be trained in the use of Truenat. Training will be delivered using a training package of presentations and video materials. The training will also include hands-on training with the Truenat devices using de-identified sputum remnants with known geneXpert results. These sputum remnants will be provided by the UGM laboratory. Staff trained to use Truenat will include ZTB YY active case finding laboratory staff and health care workers who will be involved in delivering TB active case finding in Sleman and Yogyakarta City using Truenat; as well as Universitas Gadjah Mada laboratory staff; and selected health facility staff from government health facilities in Sleman and Yogyakarta City.

All individuals who are trained will be invited in person by a member of the study team to be participants under objective 1a at the start of the training, will be provided with the PICF and will have until the end of the training to consider participation.

Training proficiency assessment components will include:

i. Observation of 'hands-on' operation of test and software using an observation checklist (see appendix 5). This will be carried out in-person by a qualified trainer. The trainer will then observe the user perform the test and score the trainee's proficiency against each of the key criteria in the checklist. Proficiency testing will be conducted for all users directly after the initial training is delivered, and then again 1 month into the intervention period. Users will need to achieve a fully correct score on proficiency testing before they are approved to operate the test in routine practice and must repeat the training and test until they obtain an adequate proficiency score. In the case of repeat testing at baseline (immediately after the initial training), only the first test done by a user will be included in the baseline analysis.
ii. An assessment of user understanding of Truenat testing fundamentals and troubleshooting actions. Shortly after conducting the observation checklist described above, the trainer will administer a questionnaire to the user to assess understanding of key aspects of the training (see Appendix 6).

The capability of laboratory and non-laboratory personnel to proficiently operate the test will be determined by calculating the proportion of users who meet performance targets after initial training.

1b Operational performance of Truenat as measured by platform failure rates and error rates

The logs from each device will be extracted by a member of the study team without patient identifying information. This data will be analysed to determine the number of tests performed, platform failures, errors and indeterminate results. In addition, electronic records will be maintained by laboratory staff conducting Truenat testing on the number of tests done, results and retests required, as well as logs of any outage time and the reason (e.g. device failure, battery depletion). Truenat operational performance will then be assessed using:

i. Truenat platform failure rates (the proportion of total working hours that the platform failed to be operational due to any reason). This will be calculated as total platform failure rate using the amount of time that assays cannot be performed due to a failure of one or more of the Truenat devices.
ii. Truenat error rates (the proportion of tests with an error result, disaggregated by error type).

1c Instrument User and health service provider views regarding feasibility and acceptability of decentralised Truenat

Views on the acceptability and operational challenges of Truenat will be assessed by a survey of laboratory staff and healthcare workers (HCWs) within the program. The survey will be divided into two sections with one section to be completed by HCW if they perform the Truenat test; and the second section to be completed by staff who are involved in registering, interviewing and assessing screening participants. Staff who work in the provision of mobile active case finding services that include Truenat testing in Sleman and Yogyakarta City will be invited, as well as lab staff who perform the Truenat tests and health facility staff at facilities where patients tested with Truenat are diagnosed and started on treatment. These staff will be contacted with an invitation to participate via Whatsapp or email. The invitation will provide a summary of the study and the purpose of the survey, as well as a unique survey link which will ensure that each staff member can only complete the survey once. The survey link will direct potential participants to a REDCap survey with an electronic PICF as the initial page. The potential participant must complete the consent form electronically with a signature before they can access the anonymous survey. The survey will be made live for one month and participants can exit the survey without consenting and later return to complete the consent process at any time during that month if they wish to participate. The survey will assess general satisfaction, ease of use, confidence in the results compared with standard of care, and problems/challenges to active case finding of use of Truenat (including HCW perception of acceptability to patients) and will include structured questions as well as open-ended questions.

1d Screening participant views regarding acceptability of point-of-care Truenat performed within mobile active TB case finding service

Views of study participants will be obtained regarding the acceptability of point-of-care Truenat through individual in-depth qualitative interviews. Purposive sampling will be used to include a diversity of sex, age, whether tested microbiological positive or negative and household contacts and community participants. Interviews will be administered 1-7 days after the initial screening. Interviews will be conducted by a researcher experienced in qualitative interviewing who is separate from the active case finding/screening team. Selection of individuals to approach will be done by the researcher working with the database manager to find people enrolled within the preceding 3 days matching specified criteria. The researcher will contact the participant by telephone, with a maximum of up to 3 phone attempts. If the participant answers the call, the reason for the call will be explained and the person will be invited to participate in a telephone

interview with an explanation that this will take up to 45 minutes either to be done at this time or at a time within the next 3 days convenient to the participant.

A telephone interview will be used as this is deemed to be less time consuming and is easier for people with the ongoing impact of COVID-19 on travel movement in Yogyakarta. Verbal informed consent will be obtained. The interview guide is outlined in Appendix 7. The person will be asked whether the interview can be recorded. If the participant agrees the call will be recorded and transcribed after which the call recording will be deleted. If the participant does not agree to call-recording the interviewer will take notes. The transcription and/or notes will have a unique identifier that is not the participants name, along with age and sex recorded. No other potentially identifying information will be recorded. As compensation for time spent contributing to the study via the interview, at the end of the interview, participants will be sent an electronic phone credit voucher to their phone number.

5.4.2 Objectives 2 and 3

Baseline Visit

Participants attending the TB active case finding service who screen positive for potential TB by symptoms or chest X-ray will be invited to participate in the study. A study team member will explain the participant information and consent form (PICF) in person and participants who consent to participate will sign and date the PICF. For participants who are illiterate, thumbprint, witness signature and date will be recorded on the PICF. Persons who do not consent to participate in the study will receive standard of care diagnosis (submit a single sputum specimen for central GeneXpert laboratory testing) and their results will not be included in the study. Potential participants have the time between the initial invitation to participate and the cessation of TB screening by the mobile active case finding service on that day to decide whether they wish to participate.

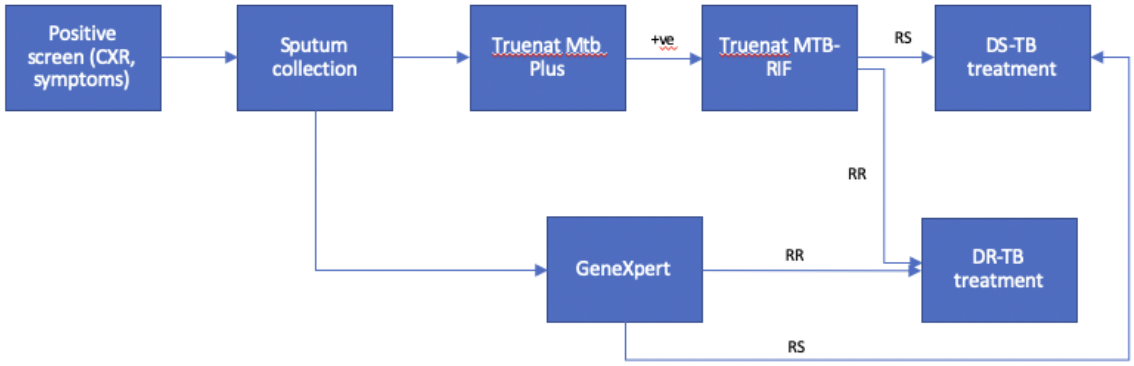
Data on study enrolment will be entered into a study-specific enrolment instrument in the ZTB YY active case finding REDCap database. The instrument will record the person's patient ID as well as their study ID and the details of their consent.

A nurse will discuss with the participant the potential that they have TB and that they require further testing for TB. They will have the process for sputum sample collection explained and spot sputum samples will be collected under observation following a standard approach for ensuring good quality sputum collection and infection control. Depending on the diagnostic

strategy assigned for the particular screening day the participant will receive either standard of care or decentralised Truenat testing:

- For **standard of care** participant samples will be sent to a centralised laboratory for GeneXpert testing. The participant will be informed that they will be notified of their results when they become available in 1-3 days. Those with GeneXpert MTB positive results will be informed by telephone to attend the nearest puskesmas for counselling and commencement of TB treatment. Those testing GeneXpert negative for MTB will have their case reviewed by the doctor at the health facility for their catchment to determine if they need further follow up or not in accordance with the standard ACF protocols.
- For decentralised **Truenat**, two spot sputum samples will be collected and the participant will be informed that their sample will be tested on the day, and will be asked if they prefer to wait for the result or be contacted when the result is available.
    - Where a patient has a positive result on Truenat MTB Plus, the Truenat MTB-RIF Dx assay will be performed to test for rifampicin resistance. Patients with a positive result on Truenat MTB Plus will be informed of the result and advised to attend the nearest puskesmas or hospital for counselling and commencement of TB treatment, or referral to another facility of their choice for treatment.
    - Those testing negative for MTB will have their case reviewed by a doctor at the catchment health facility to determine if they need further follow up in accordance with the standard ACF protocols; and taking into consideration the result of the GeneXpert MTB/RIF assay
    - Due to National Tuberculosis Program requirements all patients tested with Truenat will also be tested with GeneXpert MTB/RIF using the second spot sputum sample. Treatment will be initiated based on positive Truenat or GeneXpert Mtb/RIF result, with review by the TB active case finding service doctor of cases where the result is discordant.
    - Commencement of TB treatment will be according to standard national TB protocols. Further clinical care and diagnostic investigations will be provided within governmental health care services. If a patient wishes to seek further care at a specific health facility or service of their choosing they will be provided with a referral.

THE TESTING AND TREATMENT ALGORITHM FOR PATIENTS IN THE TRUENAT ARM



Follow-Up Interview

Participants will be called at a 14-day phone visit (+/- 7 days). Three attempts will be made to contact a participant by phone. In the event that the participant is still not contacted, a phone call to the agreed trusted contact will be made to find out about the participant's whereabouts and to ask if they can arrange for the participant to return a call or to be visited at an acceptable time. A home visit will be conducted for those participants who cannot be reached by phone or who identify that they prefer a home visit or do not have access to a phone.

The phone visit or in person home visit will repeat the symptom screening questions, as well as ask about whether TB was diagnosed, how TB was diagnosed, when the participant was informed about the TB results, if and when the participant attended the health care service (Puskesmas, private or other) and if TB treatment had been commenced.

5.5 Truenat arrangements

5.5.1 Truenat Storage

The devices, consumables and reagents for the Truenat assay will be stored in a secure, environmentally controlled and monitored area in accordance with the labelled storage conditions. Access to the storage site will be limited to authorised study staff.

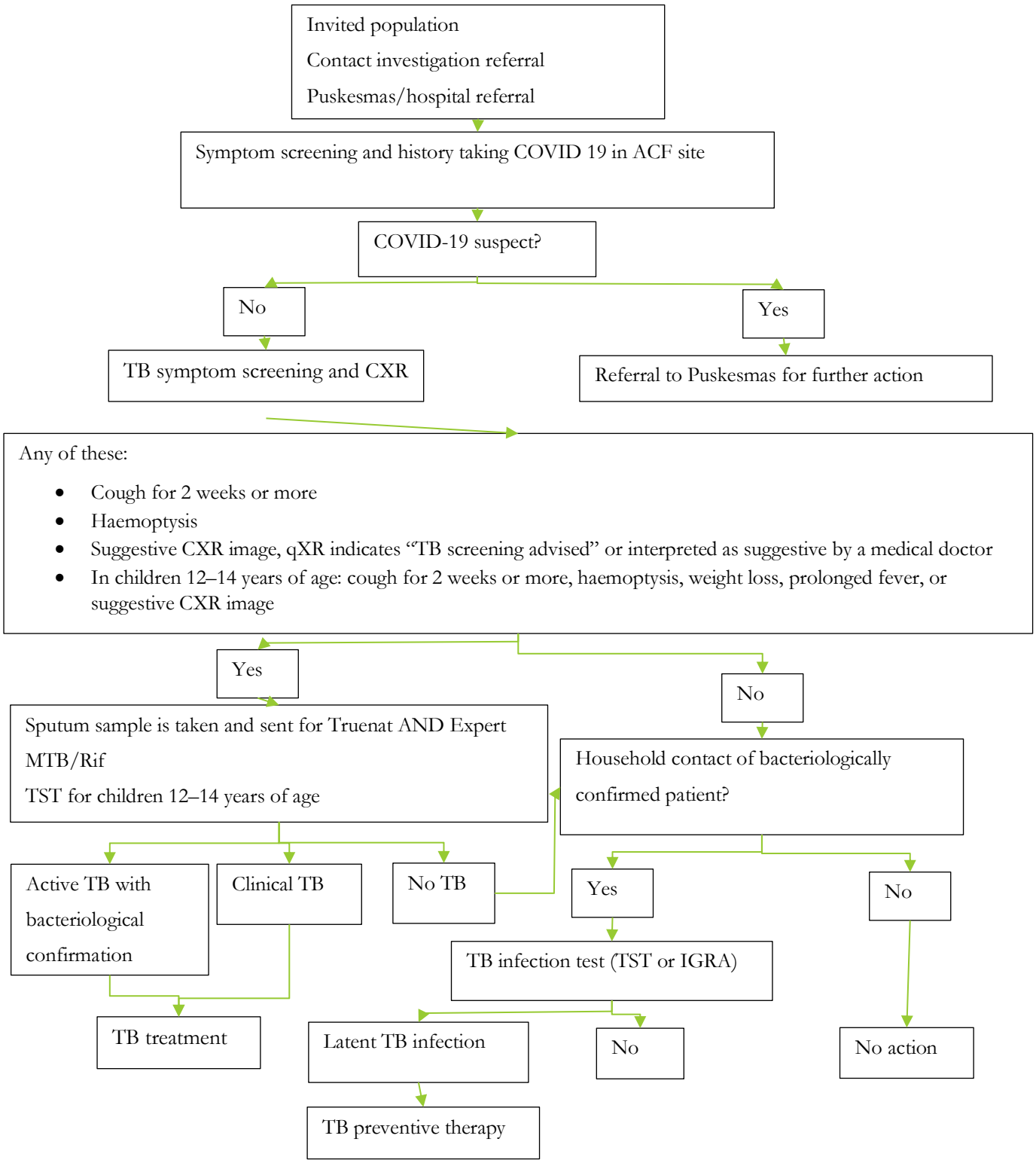
5.5.2 Truenat Test performance

Truenat testing will be performed according to the manufacturer's instructions, as detailed within the study manual. Only authorised site staff who have been trained and assessed as competent will perform sample processing. Only sputum samples obtained for the purpose of this study from participants who have provided informed consent will be processed with Truenat.

5.5.3 Accountability

The principal investigator is responsible for trial intervention accountability and record maintenance (receipt, reconciliation, final disposition). Accountability logs will be maintained within the study to ensure appropriate handling and follow up of used, failed and unused Truenat chips. Procedures for accountability will be documented in the study manual of operating procedures.

5.6 Study screening and diagnostic algorithm



5.7 Outcome Measures

Primary Endpoint

1. The operational feasibility of point-of-care Truenat, which will be assessed by:
    a. Adequacy of Truenat training as measured by post-training assessment
    b. Operational performance of Truenat as measured by platform failure rates and error rates
    c. Instrument User and health service provider views regarding feasibility and acceptability of Truenat.
    d. Screening participant views regarding acceptability of point-of-care Truenat performed within mobile active TB case finding service

Secondary endpoints

2. Median time from sample collection to result for Truenat compared to centralised GeneXpert Mtb/RIF
3. The median time from sample collection to treatment initiation for Truenat compared to centralised GeneXpert Mtb/RIF

5.8 Data Collection and management

5.8.1 Data management plan

Formal documentation, in the form of a data management plan will be finalised before the start of enrolment and will specify which roles in within the study team will have access to and responsibility for different levels of data. It will also specify the circumstances in which data may be accessed and the procedures for storing, backing up and accessing data.

5.8.2 Objective 1

1a Post-training test

A REDCap database will be set up to record the results of the post-training proficiency assessments conducted immediately after the training and at one month following the start of testing with Truenat. During data collection for objective 1a, data will be stored with the participant's name so that the results of the initial and follow-up proficiency assessments for each participant can be linked together. At the completion of data collection for objective 1a,

names will be removed from the database and only a unique study ID and details of the participants role will be retained.

1b Failure and error rates

A REDCap database will be set up to log operational hours and platform failures:

- Date of screening
- Expected / intended duration of Truenat testing for that date
- Number of hours that platform was unavailable
- Which device failed
- Type of failure
- Remedial action required

1c User acceptability

An online REDCap survey will be set up for the survey. Each person invited to complete the survey will be provided with a unique link to prevent individuals from taking the survey more than once. Branching logic will be used to ensure that staff taking the survey are shown the appropriate sets of questions (questions relating to performing/using the assay and questions relating to the role of the assay within screening and diagnostic workflows). Survey data will be anonymous and will only record minimal detail on the role of the respondent. Responses to open-ended questions in the survey will be extracted into QSR nVIVO for qualitative coding and analysis.

1d In-depth interviews with screening participants

If the participant consents, the interview will be recorded using call recording features on the phone. As such a mobile phone designated for specific use in the study will be used for all interviews and stored in a locked filing cabinet at the Universitas Gadjah Mada when not in use. At the completion of the interview (ie on the same day that the interview is done) the audio file will be transferred to a secure Universitas Gadjah Mada file server and deleted from the portable device. Each interview will be assigned a unique ID which will be recorded alongside a minimum record of interviewee characteristics:

- Date of interview
- Interviewee gender, age

- Risk population
- Truenat result

No other identifying information about the interviewee will be associable with the interview audio, transcripts and translations.

Preference will be given to Indonesian study team members performing transcription and translation of audio recordings of the in-depth interviews with an aim to transcribe interviews within a period of 6 weeks after the interview. Third-party commercial services outside the research team may be engaged to provide transcription or translation, providing that the data handling policy of the third-party is appropriate (secure and timely) for transfer, storage and deletion of audio files, transcripts and translations. Audio recordings will remain on the UGM file server until transcription and checking are complete and the recording will then be deleted. Where transcription is performed by a third party service, the file will be transferred securely to the third party service with an agreement for the service to delete the file upon request (with the request to be made once the transcript has been completed and checked).

Transcripts will be entered into an nVIVO project along with the minimal interviewee characteristic data.

Once the last interview has been successfully transferred from the mobile phone used for interviews, a factory reset of the phone will be performed before any subsequent re-use of the phone.

5.8.3 Objectives 2 and 3

Data Collection

Data collection will be performed by trained staff delegated by the PI. Data collection on patient care will be entered into the Zero TB Initiative Yogyakarta active case finding REDCap database as per the standard of care. This database stores routine patient data for patient management as well as monitoring and evaluation and approved operational research. Each patient in the project database has a unique patient ID. For individuals enrolled in this study, a study enrolment instrument (form) will be created in the existing REDCap database that records study enrolment data (unique study ID, study date, assigned testing strategy) for patients who consent to participate in the study. The instrument and data collected using the instrument will only be accessible to study investigators such that health care workers who are not investigators do not know which patients are enrolled in the study.

Source documents

The following data will be recorded directly into the electronic patient database and will be considered source data:

- Study enrolment
- Sex
- Age
- Symptoms
- Chest X-ray screen result (qXR software screening result)
- Medical history
- TB contact history
- Truenat Mtb Plus and MTB-RIF Dx; or GeneXpert MTB/Rif results
- TB diagnosis
- TB treatment
- Adverse Events

Source data for centralised GeneXpert and Truenat results will be the original reports. The results will be entered into the patient database.

Data Entry

Data entry on screening, diagnosis and treatment will be performed by the same trained staff who enter data under the current standard of care. Data will be entered during the screening and enrolment process. Follow up of the diagnosis and treatment outcomes at day 7 will occur between day 14 +/- 1 week. Study enrolment data will be entered by a member of the study team after consent is obtained.

5.8.4 Data storage and security

All REDCap databases (patient database, study enrolment database, post-training assessment, Truenat failure logging) will be hosted on a Universitas Gadjah Mada server physically located in a secure data centre in Yogyakarta. A server at a second site in Indonesia is used to back up the data on the primary server. The servers are administered by the Universitas Gadjah Mada, including management of user access. Access to individual databases in REDCap requires user authentication and each database will only be accessible to specific members of the study team. The exception to this is the patient database used for routine program care which is accessible to

ZTBI YY staff with responsibilities for patient management; monitoring and evaluation and reporting – however these staff will only have access to study enrolment data and study-specific data if they have specific responsibilities requiring such access within the study team.

REDCap database	Content	User access control
Patient database	Details of routine care (screening, diagnosis and treatment) for TB provided to screening participants	Access as per standard of care Study team will only have the minimum access needed to the patient database to enter study enrolment details (unless they have a dual role in patient care as well as the study)
Study enrolment instrument in the patient database	Stores the study enrolment data for screening participants who consent to be included in the study A unique study ID will be kept with the unique patient ID from the patient database. This linkage will be used to attach a unique study ID to non-identifiable data extracted from the patient database. The unique study ID will be assigned automatically at data entry so that it is not known to those who are entering the data	Study team members involved in study enrolment will have permission to enter data Only the data manager and the principal investigator will have access to extract and use the study enrolment data Other than the study enrolment instrument, study team members will not have access to other information in the patient database unless as a function of other responsibilities outside the study
Post-training assessment results database	Stores the anonymous results of post-training assessment tests	Accessible only to the study team members involved in entering and analysing this data

User feasibility and acceptability survey ePICF	Stores the informed consent data for participants in the user feasibility and acceptability survey	Accessible only to the data manager and the PIs
User acceptability and acceptability anonymous survey	Stores anonymous responses to the user feasibility and acceptability survey	Accessible only to the study team members analysing the data

Truenat device logs will be routinely backed up to the Universitas Gadjah Mada Tropical Medicine secure file server.

Audio, transcripts, translations and nVIVO files for the in-depth interviews will be stored on a secure file server in Indonesia. These data will be accessible only to the members of the study team involved in processing and analysing the qualitative data. If transcription and translation is undertaken by a third-party service the audio, transcripts and translations may be stored temporarily on the service provider's servers providing that the provider's data handling policy meets security and privacy requirements, and the data will not be retained by the provider once satisfactory versions of requested transcripts and translations of each interview have been delivered.

All raw and processed study data will be retained on the Universitas Gadjah Mada Tropical Medicine server for 7 years following the completion of the study. Study data for which limited consent was obtained (objectives 1a, 1c, 1d) will be deleted after 7 years. Processed study data for participants for objectives 2 and 3 who give express consent for secondary use of the data will be permitted to be used for future ethics-approved studies and will be retained for 7 years after the completion of the last study using that data and then deleted.

The data on study participants that is extracted from the patient database will be considered to constitute the study data. However, the source data – the program patient database – will be considered as routine medical record data and will be retained in accordance with Indonesian policy and legislation that require retention of medical records for a minimum of 25 years from the last entry.

5.8.5 Data Extraction

Study data will be extracted from study-specific REDCap databases for platform availability and Truenat training proficiency assessment. For objectives 2 and 3, data will be extracted from the program patient database and provided to the members of the research team undertaking data checking, cleaning and analysis. The data will be exported with only a study ID and no other identifying information. Only the data manager for the study and the principal investigator will be able to perform data extraction for the study and can only do so using scripted tools that ensure the extracted data is not identifiable.

Truenat device logs will be exported from the devices and stored on a secure file server. These will be used for platform error rates.

5.9 Sample Size

5.9.1 Objective 1: Operational Feasibility and Acceptability

1a Post-Training Assessment

All laboratory staff trained in performance of Truenat who consent to participate in the study: 2 laboratory staff and 8 non-laboratory staff will be subject to analysis using post-training proficiency assessment, and questionnaire response.

1b Operational performance

The sample size for failure and unavailability will be the total number of hours that the platform is planned to be used and available (i.e., the total hours across all screening days when decentralised Truenat is assigned); and the total number of tests allocated to the Truenat arm irrespective of whether or not the test could be performed. The sample size for test errors is the total number of assays performed using decentralised Truenat.

1c Feasibility and HCW acceptability

The survey of all HCW involved in the mobile screening service is expected to yield a sample size of (10-15 HCW staff including nurses, doctors, and program implementers).

1d Screening participant acceptability

Purposive sampling will be used to target the selection of 30 participants for in-depth interviews on test feasibility and acceptability. Critical cases will be selected to represent both those given a positive TB result by Truenat and a negative TB result, those who waited for their results and

those who did not wait. Quotas will be used to include males and females, a range of ages, and a range of different screening population characteristics (urban vs rural, risk population).

The above sample size estimations for in-depth interviews are approximations only and provide a guide. The approach for this qualitative analysis is exploratory –therefore, should information be revealed that requires exploration with other groups (e.g. community leaders), then additional in-depth interviews may be undertaken.

5.9.2 Objectives 2 and 3: Randomised comparison of decentralised Truenat MTB Plus and MTB-RIF Dx to standard of care

The mobile service screens 1000 people per month with 12.1% of participants in rural areas screening positive and requiring microbiological examination of sputum samples. We will enrol participants for a minimum of 6 months and a maximum of 9. Which would result in between 3000–4500 persons screened in each arm. Consequently, per the calculations below, the sample will be sufficiently powered to detect a difference in median time to result of one or more days with an alpha of 0.05 and power of 0.8. This would require a minimum of 211 microbiological examinations in each arm. Throughput in of 3000–4500 persons would be expected to result in 363–544 microbiological examinations in each arm.

Median time to result standard of care	Median time to result Truenat	Alpha	Power	Sample size per arm
3 (sd = 14)	1 (sd = 14)	0.05	0.8	29
3 (sd = 21)	1 (sd = 21)	0.05	0.8	34
3 (sd = 14)	2 (sd = 14)	0.05	0.8	175
3 (sd = 21)	2 (sd = 21)	0.05	0.8	211

These assumptions are based on the current active case finding TB diagnostic cascade from the PRIME-TB/TB REACH project in Yogyakarta in 2020 and 2021, which includes the impact of COVID-19 on activities.

5.10 Statistical methods and data analysis

Data endpoints for quantitative analyses and the means of calculating the proportions are summarised in table 1. For objectives 2 and 3 endpoints will be compared between Truenat and standard of care.

Cleaning and analysis of quantitative data will be conducted using R (The R Project for Statistical Computing, v4.1.2). QSR nVIVO will be used to support the coding and analysis of qualitative data.

5.10.1 Objective 1

Objective 1a

Proficiency in performing testing using Truenat Mtb Plus and MTB-RIF Dx will be assessed for all persons who undertake the training. The proportion of users who were proficient in their first post-training test will be calculated. Score summaries will be analysed as descriptive data. Among those who did not pass their first post-training, proportions will be calculated for failure for each of the competencies in the checklist. The median number and range for the number of repeat tests until proficient will be calculated for those who fail their first test.

Objective 1b

Descriptive statistics will be calculated for the number and proportion of hours that the platform was unavailable due to failure, with further disaggregation of failure by the reason for the failure. Descriptive statistics will also be calculated for the proportion of assays with an error, with disaggregation by error type.

Objective 1c

Survey data from closed-ended user feasibility and acceptability survey questions will be analysed to produce contingency tables and plots of the data, while open-ended survey questions will be coded and analysed qualitatively using a thematic approach.

Objective 1d

Patient in-depth semi-structured interviews will be analysed thematically: transcripts will be translated from Indonesian and coded using previously identified thematic codes from survey and interview guide development as well as codes that emerge during analysis. All coding will be done by at least two researchers, aiming for independent review followed by consensus through

discussion. Themes and findings will be analysed both separately (users, HCWs and patients) and combined as a means of cross verification. QSR NVivo will be used to support the coding and analysis of qualitative data.

5.10.2 Objectives 2 and 3:

For study participants who are tested using a TB molecular diagnostic test, the median time from sample collection to result will be calculated and a test of significance will be performed on the medians from the standard of care group and the Truenat group. The expected number of patients diagnosed with bacteriologically confirmed TB is expected to be too small to give sufficient power to detect a difference in median time to treatment start in these patients. Nonetheless, the median time from sample collection to treatment initiation will be calculated for the two groups. Time to event analyses will be described by Kaplan-Meier-curves by diagnostic arm. Details will be presented in the Statistical Analysis Plan.

Interquartile ranges (IQRs) and box and whisker plots will be generated for all medians, with differences in medians compared using the Wilcoxon signed rank test (Mann-Whitney *U*). Interim data analysis will occur at the study mid-point, with results reviewed by the study team.

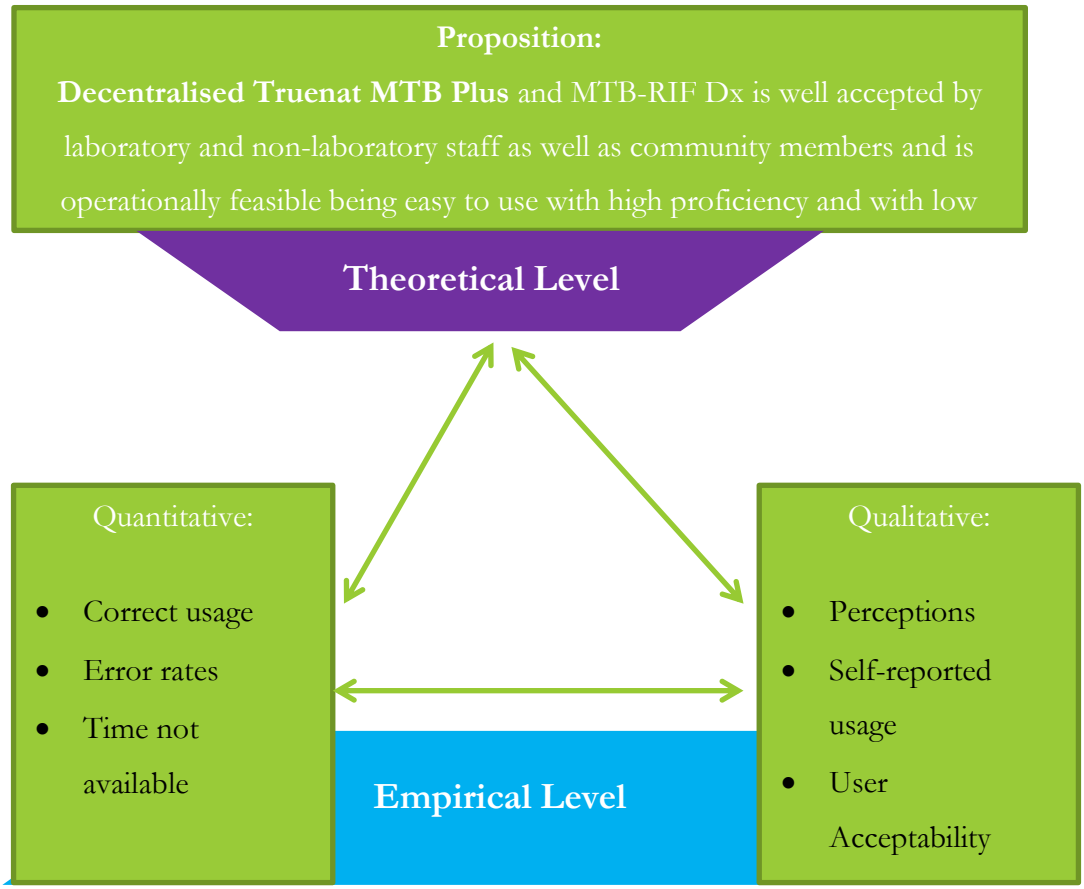
TABLE 1: ENDPOINTS AND DATA SOURCES

Endpoint	Numerator	Denominator	Data source
Objective 1			
Proportion of staff trained who were deemed proficient	Staff trained achieving proficiency in post training assessment	All staff trained	Post training assessment
Proportion of tests performed with an error	Number of Truenat tests with error or invalid result	Number of Truenat tests performed	Mobile ACF service error form
Proportion of time of device unavailability for use during	Time (hours and minutes) of device unavailability during Truenat screening	Time (hours and minutes) during screening days when Truenat	Mobile ACF service laboratory availability records

working day	days for any reason	randomized to be available	
Objectives 2 and 3			
Median time to diagnostic test result for participants tested with a TB molecular diagnostic test			Active case finding database (Redcap) Laboratory database
Median time to treatment initiation for participants with an initial positive result on a TB molecular diagnostic test			Active case finding database Pusksemas Database Week-1 telephone call

Mixed-Methods Analysis and Outputs

For the feasibility and acceptability assessment a mixed methods framework will be used. Each component of the study will initially be analysed individually in parallel. The mixed methods analysis will use the triangulation framework described by Erzberger and Kelle. (Tashakkori & Teddlie, 2010) This will facilitate a discussion of the relationships between the qualitative and quantitative data sets and the theoretical concepts underpinning the study. The theoretical framework is highlighted in the diagram below.



The combination of the quantitative and qualitative analyses allows triangulation of the data with the theoretical proposition thereby strengthening the overall analysis and interpretation. Triangulation is a process of using different methods to study a problem, thereby achieving a deeper exploration of observations and perceptions to build a more complete picture than each method would be able to provide individually. (O'Cathain, Murphy, & Nicholl, 2010) Through this process an exploration can be undertaken to look for: convergent findings which are similar findings between the qualitative and quantitative aspects or divergent findings where for example users might report ease of use, however be observed to have difficulty with certain aspects of the test. The results from the different feasibility and acceptability analyses will be synthesised giving equal weighting to each type of analysis. The investigators will review the findings from the analyses and discuss as a team to seek to understand the potential logical relationships between the observed data, the interview findings and the theoretical proposition.

6 Ethics and community engagement

6.1 Basic Principles

The study will be performed in accordance with the study protocol, national regulations, and the ICH-Harmonised Tripartite Guideline for GCP E6 (R1) (1996).

6.2 Informed Consent

Informed consent will be obtained from all participants in Bahasa Indonesia. Information on the study (participant information and consent forms; telephone scripts; and invitations to participate in the study) will be provided in Bahasa Indonesia by Indonesian study staff who are native speakers.

6.2.1 Objective 1

Written informed consent will be obtained from study participants in objectives 1a. A member of the study team will administer the participant information and consent form to all laboratory staff and health care workers undertaking the Truenat TB training that is offered in relation to the study. The PICF will be administered at the start of the training. Study procedures, anticipated benefits, the nature of participation and potential risks will be explained as well as the right to withdraw from the study at any time. Participants can decide to participate at any time prior to the commencement of baseline post-training proficiency assessments. Trainees will be qualified health workers and the PICF will be written and administered using suitable language and therefore it is expected that for objective 1a, literacy will not be a barrier to obtaining informed consent from the participants.

For objective 1c, electronic informed consent will be obtained from all participants. Prospective participants will be sent a unique link to a REDCap web survey for the participant information and consent form. Those wishing to participate must complete the consent form with an electronic signature. Prospective participants will have the option to leave the survey before consenting and return to it at any time during the one-month period that the survey will be open. This includes leaving to obtain more information to decide whether to participate and returning if then deciding to participate. Upon completing the electronic consent form – which will include a signature – the participant will then be forwarded to a separate, anonymous REDCap web survey for the feasibility and acceptability survey. As survey invitees are qualified health workers,

literacy is not expected to be a barrier to obtaining informed consent from participants in the feasibility and acceptability survey.

For objective 1d, verbal consent will be obtained over the phone by the interviewer prior to starting the interview. A phone script will be used to provide information to the potential participant and will provide a brief summary of the study purpose, procedures, what is involved in participating in an interview, the right not to answer questions in the interview and the right to withdraw from the study at any time. The prospective participant will be able to ask the interviewer any questions they might have about the study and participation in it before deciding whether to participate; and to schedule the interview for a time that is convenient for them. A participant will have the right not to answer any question that they would prefer not to; and to end the interview at any time and for any reason. The participant can review or modify their response at any point up until the end of the interview. Once the interview is completed, because the recording will be stored without identifying information it will not be possible for the participant to then review or withdraw their data from the interview.

6.2.2 Objectives 2 and 3

Objectives 2 and 3 of this study are taking place within a mobile TB active case finding service. Those who screen positive will be asked to provide informed consent for participation in the study. They will be provided with a participant information sheet and consent form (PICF) about the study. A study team member designated by the principal investigator will administer informed consent. The study procedures, anticipated benefits and potential risks will be explained. The language used will as far as possible be non-technical. As part of the consent process, it will be explained that participation will require that participants allow the extraction of their source data from the screening service for use in the study. Extended consent to use the data for secondary use of the data (but not specimens) will be sought from these participants and they can choose not to consent to the secondary use of the data and allow their data to be used only for this specific study.

Potential participants will be informed that as they have screened positive by symptoms and/or chest x-ray they should have further testing for possible TB. This will involve supervised collection of a sputum specimen. The sputum specimen will either be tested at a centralised laboratory with geneXpert MTB/RIF or will be tested onsite with DTMP. Participation in the study is voluntary. Those choosing not to participate in the study will receive standard of care with sputum samples referred centrally and their data will not be used in the study analysis.

Participants will be able to withdraw from the study at any time, and this will not have any effects on them receiving standard of care following withdrawal.

For those who are illiterate, study information will be given in the presence of an impartial, literate witness. The information sheet will be read to the person. Consent will be given by thumb print on the PICF, and the witness signing on the PICF that free, informed consent has been given.

6.3 Confidentiality

Only reidentifiable data without personal information will be extracted from the source data for the quantitative analyses.

No identifying information about interview participants will be used in the study.

All study staff will be trained in ICH GCP standards and the importance of maintaining confidentiality and will hold a GCP accreditation/certificate

6.4 Benefits and implications for policy and practice

Truenat is a WHO recommended TB diagnostic test. This study is expected to provide valuable information about the feasibility and acceptability of the decentralised use of this test within the mobile active case finding service. The study will provide information on the potential diagnostic and therapeutic benefits of use of Truenat within the screening service. The study will directly inform the decision making of the Indonesian Government for scale up of TB mobile screening services.

Some specific benefits of the use of a TB point of care test may include:

- Facilitating faster diagnosis and treatment initiation
- Reducing the risk of transmission in the community by starting TB patients on treatment earlier.
- Decreasing the number of people who are lost-to-follow-up during the diagnostic process
- Reducing workload for screening staff needing to follow up on lab results and finding and informing patients after they have been screened.

6.5 Potential Risks

The risks of involvement in the study are minimal for study participants.

For objective 1a, the main risks are:

- Undertaking the post-training proficiency assessments is required operationally but inclusion of the assessment results in the study is voluntary. This could result in confusion about this distinction and care will be taken to explain it to participants
- Potential participants may be employed by the same organisation that is conducting the study and feel compelled to participate as a result. Care will be taken to distinguish between responsibilities as an employee (undertake training, undertake post-training proficiency assessments and conduct testing of patient samples using Truenat during the study period) and participation in the study (have their proficiency assessment results recorded and used in the study). Moreover, it will be made clear that participation is voluntary and choosing not to enrol as a study participant will not affect their employment

For objective 1c, as the survey is voluntary and anonymous, there are no risks of substance that are expected in responding to the survey. Survey data will be analysed and reported in aggregate and any qualitative data will be reported with attribution that will not reveal the identity. Agreement of employers for their staff to undertake the survey will be arranged so that staff can respond to the survey within their work hours.

For objective 1d, there is a risk that some of the subjects discussed in the interview relating to experience of TB services and diagnosis of TB could be emotionally distressing and upsetting for some interviewees. Interviewees will be informed that they do not have to answer a question if they do not wish to and that they can end the interview at any time. In addition, the phone script to be read by the interviewer at the start of the call informs the participant that the interviewer can refer them to nurse health educator and counsellor for support in the event that the interview causes the interviewee distress.

For objectives 2 and 3, there is an additional burden of time and slight physical discomfort for participants in the Truenat arm as they will be requested to produce an additional sputum

specimen. However, the sputum collection process is non- invasive, and will be performed in accordance with national guidelines, in order to minimize airborne infection control risk. As part of the active case finding service, participants are screened for symptoms suggestive of potential COVID-19 and referred for further assessment if screening positive for potential COVID-19. Participants do not come into contact with any study device or test, as testing is being performed upon sputum specimens.

The risks to users who will be operating Truenat are minimal and will be undertaken in the context of routine service delivery. Opening of the specimen container prior to the addition of SR Buffer only exposes the staff member to the same minimal risk as for sputum microscopy, and this risk is negated if the user follows protocol correctly. The addition of the SR buffer to the specimen renders *Mycobacterium tuberculosis* and other organisms inviable after 15 minutes of incubation at room temperature. Additionally, the test will be performed in a designated area with good ventilation and separated so that other staff or participants or community members cannot enter, and the staff will be wearing N95 respirators.

6.6 Community engagement

As part of the mobile TB active case finding service, community stakeholders will be informed about the screening. As part of this process sensitization about the study will also be provided, in the context of the study being conducted as part of routine active case finding services.

6.7 Safety and Incident reporting

The principal investigator and qualified designated staff are responsible for detecting, documenting, reporting and following up any events that meet the definition of an adverse event (AE) or a serious adverse event (SAE).

The probability of an AE or SAE occurring to a trial participant associated with Truenat is extremely low. This study uses a WHO-endorsed assay (Truenat) with non-invasive sample collection that is not different to standard of care.

Safety reporting is therefore limited in scope to events associated with the collection of samples and those that occur while using the Truenat medical devices. Only fatal SAEs and medical device incidents fulfilling the definition of AE or SAE will be reported. The definitions can be found in appendix 3. Any fatal SAE will be reported to the study sponsor, as well as to FIND and to the ethics review boards.

6.8 Research Skills Development

Research skills building is a key component built into the study. Investment in diagnostic test and TB research capacity through training, supervision and mentoring of staff is an important objective of the Zero TB Initiative in Yogyakarta, as research is needed to help guide innovation and program improvements in order to be able to achieve the Indonesian National TB Elimination targets. This will be achieved through the inclusion of laboratory, facility, program and district/provincial health program staff in aspects of the study. This is seen in the range of co-investigators, who will work alongside investigators from UGM and Burnet Institute, gaining experience in detailed design and implementation of research activities with direct clinical and policy relevance. In addition, junior researchers may be engaged from UGM, and the study data used for their masters projects.

7 Results dissemination

The study findings will be disseminated locally and internationally. A summary of the findings of the study will be shared with the Dinas Kesehatan and local key stakeholders and with the National TB Program. Study results will be submitted for presentation at relevant national and international conferences and will be submitted for publication in a peer-reviewed journal.

8 Materials and Timeline

8.1 Study Budget

Item	**Cost**
Human Resources (research officer, medical lab scientist)	29,000
Data base set up and management	10,000
Statistical Analysis	5,000
Project manager	7,000
phone credit/IT support	2,000

patient support	1,000
logistics support	2,000
Institutional Costs	8,400
Total	USD 64,400

Funding for this study has been provided by FIND. The study will be embedded within the ongoing community mobile active case finding program (Zero TB Initiative Yogyakarta) that is funded by the Australian Department of Foreign Affairs and Trade's (DFAT) Centre for Health Security through the PRIME-TB grant. This grant provides funding for the mobile van screening team (costs for van running, chest x-ray, mobile van screening team, community mobilisation officer, technical specialists from UGM and Burnet, project manager, finance management).

In addition, provision of equipment from FIND includes:

- Trueprep AUTO v2 Universal Cartridge Based Sample Prep Device
- Truelab Uno/Duo/Quattro Real Time Quantitative micro PCR Analyzer
- Truelab micro PCR Printer
- Truenat MTB Plus chip kits
- Truenat MTB-RIF Dx chip kits
- Transport of items to Indonesia
- Training for Truenat MTB Plus

8.2 Timeline

Protocol finalisation & Ethics Clearance	Q2 2022
Importation	Q2 2022
Training + post training Assessment	Q3 2022
Participant enrolment	Q3 2022-Q3 2023
Data Cleaning + analysis	Q3-Q4 2023
Total duration 18 months	

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10 Appendix 1. User Feasability and Accessibility Survey

10.1 1A. Questions for those who have performed the Truenat test

- What is your profession, current work position?
- How long have you worked in this project?
- When did you start using the Truenat test?
- What training did you receive to use the Truenat test?
    - Describe the training you received before you could perform the Truenat test.
    - Who provided the training?
- Describe the process you follow when you consult a patient whom you think should have a Truenat test done.
- Is there a written protocol on how and when to utilise the Truenat test? (Staff to show it or mention where it can be found).
- How many patients do you consult/look after each day in the active case finding service?
- Approximately how many Truenat test tests do you perform per day?
- Where is the Truenat test performed?
- Where are the Truenat tests stored?
- What other equipment/supplies do you need to perform the Truenat test (apart from the cartridges and machine themselves?)
- How long do you wait before reading the Truenat test result (what you do in practise)?
- How do you dispose of the cartridge after performing the test?
- Do you give any information to the patients prior to performing the Truenat test?
    - Describe the information you give to the patients at this time
- In your experience, do you consider the Truenat test easy to perform, or difficult? Give your reasons.
- What are your views on performing the Truenat test relating to your daily workload?

- What are your views in relation to the introduction of the Truenat test as a TB diagnostic tool?
    - Have you experienced any benefits of using the Truenat test? What are they?
    - Have you experienced any challenges of using the Truenat test? What are they?
    - Are there delays experienced by patients in getting Truenat tests done on the same day as their sample is collected? What causes these delays?
- Do you have anything else to add with regards to the Truenat test?
- Who collects the sputum samples?
    - In your experience, how long does it take before you get back sputum results (Truenat and GeneXpert)?
    - In your experience, do the patients face any challenges in producing a sputum sample?
    - What are these challenges?
    - What are the main reasons for patients not to produce sputum?
    - Describe the process of how you send sputum samples to the laboratory for GeneXpert testing, and how you get back the result.
    - Are there any challenges you face during this process? What are they?

10.2 1B. Questions for health care staff involved in the TB diagnostic process

- What is your profession/current work position?
- How long have you worked in this project?
- Describe the regular TB screening and diagnostic algorithm for patients seen in the mobile TB active case finding service.
- Describe what happens when patients are referred for sputum submission
    - How long does it take to get a result with Truenat?
    - How long does it take to get a result with GeneXpert testing at a laboratory?

- What causes the delays (i.e. results not being reported in the minimum possible number of days between specimen collection and testing)?
- Describe the process of how you send sputum samples to the district laboratory/another laboratory for GeneXpert, and how you get back the results.
- Are there any challenges you face during this process? What are they?
- In your experience, do the patients face any challenges in producing a sputum sample?
- What are these challenges?
- What are the main reasons for patients not to produce sputum?

- For staff reporting GeneXpert and Truenat results back to participants:
  - Did you have any problems interpreting or explaining Truenat results to patients
  - Did you observe problems during the screening days when Truenat was used? If "yes", what problems did you observe?
  - Did you observe problems during the screening days when GeneXpert testing at another laboratory was used? If "yes", what problems did you observe?
  - Do you have a preference for which test you would prefer to offer within the mobile screening service? If "yes", why?

11 Appendix 2. User Feasability and Acceptability Survey Part 2 – Ease of Use

Date of response: … … … … / … … … … ./ … … … … .

To be filled by each Laboratory technician, Nurse, Doctor, who has performed the Truenat Mtb Plus and MTB-RIF Dx tests. Please complete the following sections on

Have you performed testing with Truenat Mtb Plus and MTB-RIF Dx prior to this? Yes No

Please tick applicable: Number of Truenat tests performed**: <20 tests□ >20 tests□**

Actual number of tests done if less than 20 (estimate): … … … … … .

Please comment on how you found performing each of the following activities.

Question 1: Was the activity **difficult, OR easy**?

Question 2: Do you have any comment?

Item	**Answer 1: Difficult = D; Easy = E;**	**Answer 2: Comments**
Understanding the Truenat Mtb Plus test information leaflet		
Turning on the True prep Auto device		
Preparing and adding sample to Trueprep cartridge and loading in Trueprep Auto device		
Removing Eluate from Trueprep cartridge and		
Transferring required amount of eluate by pipette to Truenat Mtb Plus chip		
Turning on the Truenat Mtb Plus Truelab micro PCR Analyzer		
Turning on and connecting the mobile device		
Entering patient ID and sample details		

Item	Answer 1: Difficult = D; Easy = E;	Answer 2: Comments
Loading chip and commencing Truelab Dx micro PCR Analyzer machine		
Reading the results		
Printing the results		
Interpretation of the result as either positive or negative for MTB		
Loading MTB-RIF Dx chip		
Interpretation of the result as positive or negative for rifampicin resistance		
Retest instructions		
Disposal of the cartridges and chips		
Disposal of the pipette		

If you were training someone on performing the Truenat test:

What are the most important things you would teach them?

If you were training someone on Reading the Truenat Results:

What are the most important things you would teach them?

General comments

- At which steps of the Truenat testing procedure do you think there may be risks of errors?
- After how many tests did you feel fully comfortable with the whole procedure (i.e. you were able to perform all steps without any hesitation)?
- In your own opinion, basing on your experience, what are the advantages of using the Truenat test in the diagnosis of TB?
- In your own opinion, based on your experience, what are the main challenges in using the Truenat test to diagnose TB?

Any other comments?

Thank you for your feedback.

12 Appendix 3: Safety Definitions and Reporting

AE Definition
• An Adverse Event (AE) is any untoward medical occurrence in a patient or study participant, temporally associated with the use of the study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study intervention.

SAE Definition
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

13 Appendix 4: Incident Definition and Reporting

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

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Medical Device Incident Documenting
• Any medical device incident occurring during the trial will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate study form. • For incidents fulfilling the definition of an SAE, the appropriate AE/SAE form page will be completed

- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device) at the time of the initial SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

15 Appendix 5: Observation Checklist for Post-training Assessment

Item	Assessment: (C) Performed Correctly (I) Incorrect Performance	Comments for Incorrect performance
Turning on the Truenat sample preparation and analyser devices and connecting the mobile device		
Entering patient ID and sample details		
Preparing chip from sample using the sample preparation device		
Loading the chip into the analyser		
Reading the results		
Printing the results		
Transmitting the results to a health facility or patient		
Interpretation of the result as either positive or negative for MTB and for rifampicin resistance		
Disposal of pipette and cartridges		
Connecting and charging device batteries		

16 Appendix 6: Post-training questionnaire for trainees

Question	Expected answer
What are the two devices that are used for the Truenat assay? What does each one do?	Trueprep and Truelab Analyser Prep prepares a chip from the sample. Analyzer runs the PCR test using the chip
What are the two types of chips? What does each one do? When should you use each one?	Truenat MTB Plus – tests for presence of Mtb and should be used for all samples referred for testing Truenat Mtb RIF – tests for presence of rifampicin resistance in Mtb and should be used only on samples that test positive for Mtb
Please list all the possible results for the Truenat MTB Plus test and explain what each one means	Valid/Invalid MTB Detected/Not detected/Error High/Medium/Low/Very low
What needs to be done to check that the Truelab Analyzer is working accurately?	Test monthly with positive and negative control (Truenat positive control kit – panel I) or PBS as negative control and known positive (from culture) as positive control
If the Truelab Analyzer gives an error, how would you work out what is causing the error?	Check the error code in the product documentation
What should you do in the event of a platform failure or outage?	Log the time that the platform is unavailable Investigate any error information and attempt to remediate, and notify the manufacturer for support if can't be resolved locally

17 Appendix 7: Screening participant interview guide

Interviewer instructions:

- Start by reading the telephone interview consent script
- Answer any questions that the person might have about the study and what participation involves
- Check whether the person consents to the interview
- Confirm a suitable time

Interview questions:

1. With your permission, I would like to record this interview? Do you give permission for me to record this interview? [If "Yes" remind the interviewee they can ask to stop recording at any time]
2. At which service were you tested for TB?
3. How did you find out about the service that you visited?
4. Why did you decide to visit the service?
5. Would you recommend to friends and family that they use the screening service? Why or why not? What was good and bad about it?
6. What was your experience like in being informed about what the test was for and what it would involve? What were you told about the tests that were performed to diagnose whether or not you have TB?
7. What was your experience like in producing a sample for the test?
8. When your sputum was tested, the health care worker should have given you the option to wait for the result on the spot or to be contacted once the test was complete. Which option did you choose and why?
9. What was your experience like in being notified of results?
10. If you didn't receive your test result on the same day that you were tested, when were you notified of the result?
11. What advice were you given at the time that you were notified of the result?
12. What action did you take based on the result and any advice you were given?
13. What could be done differently that would have made the service more useful? What could have been done to make the service more informative and easier to use?

18 Appendix 8: Serious adverse events reporting form

SAE Event term	
Date of SAE onset (Yiyi/mm/dd)	_ _ _ _ / _ _ / _ _
Date SAE stopped (yyyy/mm/dd)	_ _ _ _ / _ _ / _ _
Was this an unexpected adverse event	[] Yes [] No
Describe the SAE	
SAE Category	[] Death [] Life threatening [] Hospitalisation – initial or prolonged [] Disability or incapacity [] Congenital anomaly/birth defect [] Required intervention to prevent permanent impairment [] Other
If "Death", what was the date of death (yyyy/mm/dd)	_ _ _ _ / _ _ / _ _
Was the SAE related to the study	[] Unrelated (clearly not related to the study) [] Possible (may be related to the study) [] Definite (clearly related to the intervention)
Was the study stopped due to this SAE	[] The trial will continue without alteration [] The trial will continue with the PICF updated to reflect the amended information

	[] The trial will continue, however this report raises concerns that the Principal Investigator will monitor and report on as appropriate [] The trial will be suspended [] Other action is required (describe)
Describe the medications and steps that were taken to manage the SAE	
Name of Principal investigator Reporting the SAE	[] Philipp du Cros [] Rina Triasih
Date of report (yyyy / mm / dd)	_ _ _ _ / _ _ / _ _
Signature of Principal Investigator	