RPT 01

COMMON PROTOCOL FOR COLLECTING DATA AND BIOREPOSITORY SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) INDIA CONSORTIUM (RePORT INDIA COMMON PROTOCOL)

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LIST OF ABBREVIATIONS AND ACRONYMS

AFB	Acid-Fast Bacilli
BJ**G**MC	Byramjee Jeejeebhoy Government Medical College
BMMRC	Bhagwan Mahavir Medical Research Centre
BPHRC	Blue Peter Public Health & Research Centre
CBC	Complete Blood Count
CD4/8	Cluster of Differentiation 4/8
CHRD-SAS	Centre for Health Research and Development-Society for Applied Studies
CMC	Christian Medical College
CRF	Case Report Form
CRU	Cohort Research Unit
CTB2	Consortium for Tuberculosis Biomarkers
CTU	Clinical Trials Unit
CXR	Chest X-Ray
DAIDS	(United States) Division of AIDS
DBT	(India) Department of Biotechnology
DNA	Deoxyribonucleic Acid
DR	Drug-Resistant
DS	Drug-Susceptible
DST	Drug Susceptibility Testing
GA	Gastric Aspirate
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c (Glycated Hemoglobin)

HHC	Household Contact
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
IRB	Institutional Review Board
JIPMER	Jawaharlal Institute of Postgraduate Medical Education & Research
LTBI	Latent Tuberculosis Infection
MDR	Multidrug-Resistant
MOP	Manual of Operating Procedures
mRNA	Messenger Ribonucleic Acid
Mtb	Mycobacterium Tuberculosis
MVDRC	M.V. Diabetes Research Centre
NACO	National AIDS Control Organization
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NIRT	National Institute for Research in Tuberculosis
NP	Nasopharyngeal
OAR	(United States) Office of AIDS Research
PBMC	Peripheral Blood Mononuclear Cell

PI	Principal Investigator
PID	Participant Identification Number
PPD	Purified Protein Derivative
PY	Person-Year
RePORT	Regional Prospective Observational Research for Tuberculosis
RNA	Ribonucleic Acid
RNTCP	Revised National TB Control Programme
SOP	Standard Operating Procedure
TB	Tuberculosis
TST	Tuberculin Skin Test
TX	Treatment
TX F/R/W	Treatment Failure/Relapse/Withdrawal Evaluation
VAP	Vaccine Action Program
WHO	World Health Organization
XDR	Extensively Drug-Resistant

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PROTOCOL SCHEMA

PURPOSE: To establish a biorepository in India with an associated database of wellcharacterized specimens and standardized data for future tuberculosis (TB) research. The Common Protocol for Collecting Data and Biorepository Specimens from Participants in the Regional Prospective Observational Research for Tuberculosis (RePORT**)** India Consortium (RePORT India Common Protocol), developed for this purpose, describes the populations and processes for collecting the specimens and data.

DESIGN: Biospecimens will be stored in a Central Biorepository over time from two prospective, observational cohorts, one with participants who have active pulmonary TB (Cohort A) and the second with participants who are household contacts (HHCs) to an active case of TB, (Cohort B).

POPULATION: Participants of any age from India enrolled into one of the two observational cohorts: active pulmonary TB and HHCs.

STUDY SIZE: Approximately 1,700 participants in Cohort A and approximately 5,100 participants in Cohort B.

STUDY DURATION: Cohort A participants will be on the study for the duration of TB treatment and 6 months post-treatment (e.g., total time on the study will be 12 months if the participant's treatment regimen is 6 months). Cohort B participants will be on the study for 24 months.

PRIMARY OBJECTIVE: To provide specimens to Indian biomarker researchers and their collaborators, leading to a better understanding of the prognosis of TB disease and the pathogenesis of progression from TB exposure to the development of active disease.

SPECIMEN COLLECTION:

The following specimens for Central Biorepository storage will be collected:

Cohort A: Mycobacterium tuberculosis (Mtb) isolate subculture, whole blood (PAXgene, genetic analyses, peripheral blood mononuclear cell (PBMC), plasma), urine, sputum, and saliva.

Cohort B: Whole blood (PAXgene, genetic analyses, Interferon-Gamma Release Assay (IGRA), PBMC, plasma), urine, and saliva; sputum and Mtb isolate subculture only at TB Activation Visit.

The following tests will be performed at a local laboratory:

Cohort A: Human immunodeficiency virus (HIV) test, cluster of differentiation 4 (CD4) count (if HIV-infected), complete blood count (CBC) and lymphocyte count, hemoglobin A1c (HbA1c), sputum smear, culture, and drug susceptibility testing (DST).

Cohort B: Sputum smear, culture, and DST, HIV test, CD4 count (if HIV-infected), CBC and lymphocyte count, and HbA1c at TB Activation Visit only.

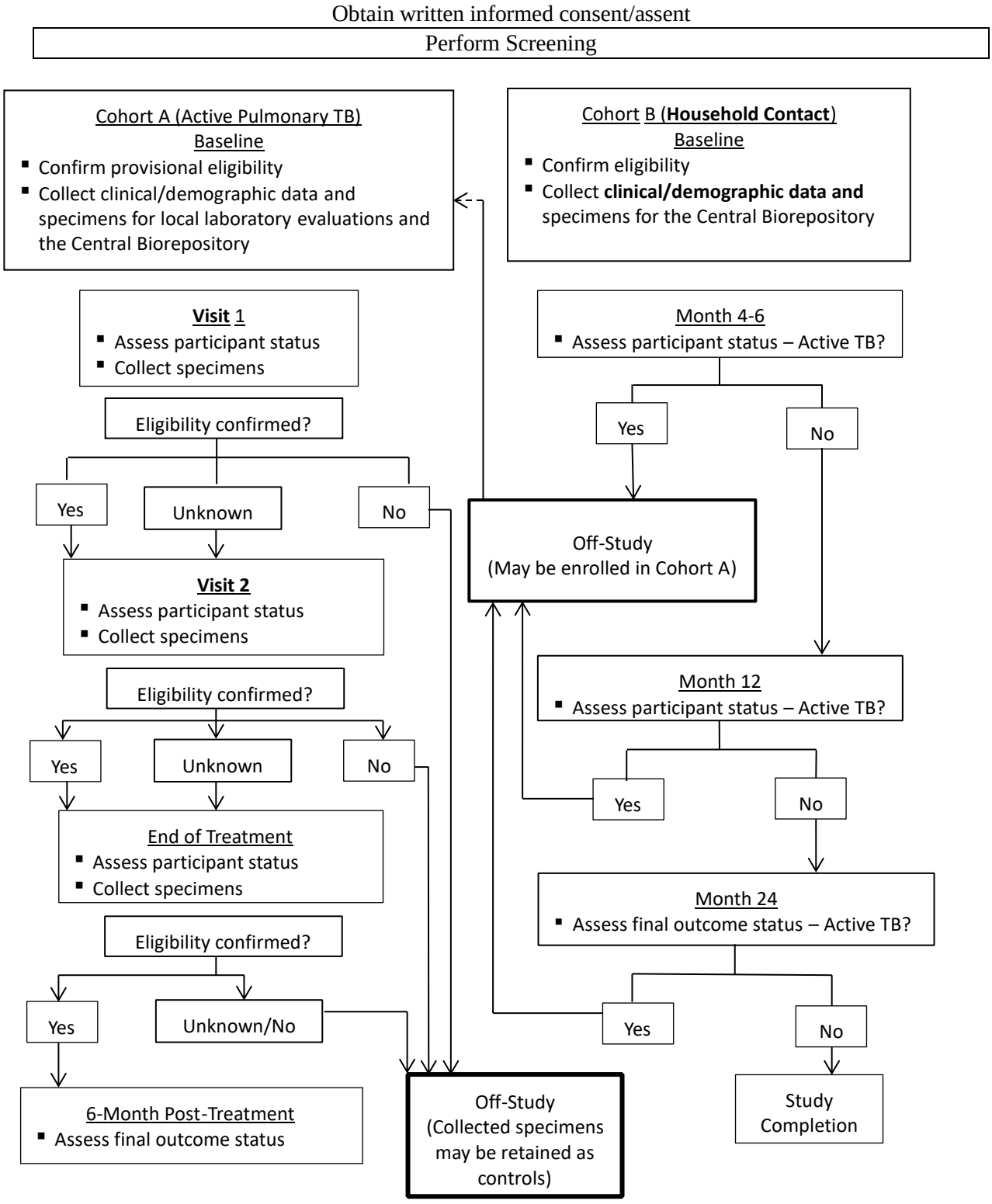
STUDY SITES: Participating study sites are located in Pune, Hyderabad, Chennai, Vellore, and Puducherry**,** India, and may be expanded to other locations.

INDIAN DATA MANAGEMENT CENTER: The Centre for Health Research and Development (CHRD)-Society for Applied Studies (SAS) in New Delhi, India.

INDIAN CENTRAL BIOREPOSITORY: National Institute for Research in Tuberculosis (NIRT) in Chennai, India.

U.S. COORDINATION SUPPORT CENTER: Westat in Rockville, Maryland, United States of America.

PROTOCOL SCHEMA DIAGRAM



1. Background

Mycobacterium tuberculosis (Mtb) causes pulmonary and extra-pulmonary forms of tuberculosis (TB) across the globe. Though an effective treatment regimen exists for most of those who become sick with TB, the regimen has significant toxicities, is lengthy, and with the increasing prevalence of drug-resistance, is more difficult to cure. In addition, many key aspects of TB infection and subsequent disease remain unknown. Investigations focused on understanding the pathogenesis of progression from infection to disease are needed, as is a better understanding of the prognosis of the disease, including biomarkers that correlate with the likelihood that a new drug or drug regimen will be effective. These investigations require biological specimens collected from well-characterized active pulmonary TB participants and household contacts (HHCs) of infectious TB cases who are at risk of progressing to active TB disease. These specimens could then be made available for a variety of purposes, including development of biomarkers. There is no theoretical barrier to finding such valuable biomarkers. What is needed is a high-quality Central Biorepository of clinically well-documented and relevant biological samples, collected serially from participants from the time of diagnosis, to a final determination of outcome status.

1.1 Rationale

Progress in TB clinical research is hampered by the lack of reliable biomarkers to serve as a surrogate endpoint predicting efficacy of prevention and treatment modalities. Human immunodeficiency virus (HIV) antiretroviral treatment research, in contrast, has greatly benefited from the HIV viral load biomarker. There is currently no substitute for sputum culture conversion for predicting efficacy of new candidate vaccines, drugs, and drug regimens. In addition, biomarkers that predict progression from TB exposure to active disease are needed to advance TB prevention efforts, both in vaccine development and treatment for prevention.

The Indian Department of Biotechnology (DBT), Ministry of Science and Technology; Indian Council of Medical Research (ICMR); U.S. National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS); and CRDF Global are cofunding five teams of India and U.S.-based investigators, to perform individual cohort studies of active pulmonary TB and HHCs of infectious TB cases. The newly organized Indo-U.S. Vaccine Action Program (VAP) Initiative on Tuberculosis Research: The Regional Prospective Observational Research for Tuberculosis **(**RePORT**)** India presents a new and valuable opportunity to create an Indian owned and managed TB biorepository.

1.2 Study Objective

The primary objective of the study is to provide specimens to Indian biomarker researchers and their collaborators over the next decade to achieve a better understanding of:

- The prognosis of TB disease; and
- The pathogenesis of progression from TB exposure to disease.

Other teams around the world are establishing repositories aimed at understanding whether or not a new drug or drug regimen is likely to be effective, but the main purpose of this biorepository is broader than that.

1.3 Description of the Population

The India-U.S. investigator teams are poised to enroll the following populations into their sitespecific protocols: approximately 2,600 adults and children with active pulmonary TB; approximately 6,700 recent HHCs at risk for progression to active TB; and approximately 410 healthy community controls. Enrollment into site-specific protocols began in 2014. Of those who will enroll into site-specific protocols, approximately 1,700 participants with active pulmonary TB will enroll into Cohort A, and approximately 5,100 HHCs will enroll into Cohort B of the Common Protocol. Based on research and programmatic experience, it is estimated that these cohorts will yield between 85 to 170 episodes of relapse or failure of treatment among the active pulmonary TB cases, and approximately 255 cases of active pulmonary TB among the recent HHCs (see Section 7, Sample Size). The RePORT India Common Protocol will enroll participants who may be concurrently enrolled in a participating Cohort Research Unit (CRU) ongoing "Parent" Protocol and/or other approved studies (see Section 3.1). The intention of this Common Protocol is to provide a mechanism by which each CRU is responsible for collecting pre-determined clinical data and biological specimens at specified time points, using a unified protocol and standardized methods. When possible, these specimens will dovetail with specimens that CRUs need to collect to meet their own investigation endpoints, though there may be additional time points or specimens needed to complete the Common Protocol requirements.

2. Study Design

There will be two prospective, observational cohorts developed: one with participants who have active pulmonary TB (Cohort A) and the second with participants who are an HHC to an active pulmonary TB case (Cohort B). This protocol has been designed to provide a uniform schedule and methodology for collecting clinical data and specimens from participants in each cohort so that they can be placed in biostorage for future studies. The samples will be curated, stored, and managed at the Central Biorepository. The resultant Central Biorepository of biological samples will be made available to investigators participating in or collaborating with the RePORT India Consortium through a peer-review process that considers high-priority, credible proposals for their use. Samples collected for each CRU's Parent Protocol are to be kept separate from the Common Protocol, are not to be co-mingled with, or expected to be extracted from samples at the Central Biorepository. Example uses for stored specimens include but are not limited to[1]:

1. Mtb isolates for full genome sequencing for virulence factors, association with clinical outcomes, and in the case of relapse, for comparison to the baseline specimen.
2. Plasma for proteomics, metabolomics, lipidomics, and noncellular measures of immune response (e.g., cytokines, chemokines).
3. Whole blood for transcriptomics, whole genome sequencing, and other genetic analyses.

4. Whole blood stimulated with mycobacterial antigens yielding supernatant to be stored for measuring noncellular immune responses (e.g., cytokines, chemokines).
5. Peripheral blood mononuclear cells (PBMCs) to measure cluster of differentiation 4 (CD4), CD8, and other cellular immune responses.
6. Urine for metabolomics and measures of microbial markers.
7. Sputum for messenger ribonucleic acid (mRNA), microbiologic measures, and host immune markers.
8. Saliva for transcriptomics, whole genome sequencing, and other genetic analyses.

While this valuable resource will be primarily for use within India, it is expected that the samples in the Central Biorepository will also be available to investigators external to the RePORT India Consortium, if approved by the RePORT India Consortium and with the appropriate ethical and scientific approvals.

Since this study requires collection of additional samples and testing beyond what is normally collected or tested for participants being treated in the Revised National TB Control Programme (RNTCP), IRB/IEC approvals will be required. Because of the rapidly developing science in this field, it is not possible to predict precisely which tests will be performed with these samples. In addition, many important discoveries are likely to be made through the analysis of human deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and thus informed consent for this use will also be sought, which will include subsequent testing for genetic markers.

2.1 Co-Enrollment Guidelines for Cohort A and Cohort B Participants

The protocol leadership must approve co-enrollment into other clinical studies and enrollment into the Common Protocol if participants are already enrolled in a study other than the Parent Protocol at the time of screening. See the RePORT India Manual of Operating Procedures (MOP) for details.

3. Cohort A: Participants with Active Pulmonary TB

3.1 Design and Procedures

Participants being recruited in the context of a study developed and approved by the RePORT India Consortium (e.g., Parent Protocol) will have the option of participating in the Common Protocol. Other individuals with suspected TB who are referred to the CRU may also participate in the Common Protocol. Participants who voluntarily agree to take part will be required to sign a Common Protocol informed consent form (ICF) before they can be screened for eligibility. Assent forms will be signed by children, as required by the local IRB/IEC, accompanied by an ICF signed by their parents/legal guardians (see Appendices A and B). Those that sign the ICF/assent form, meet eligibility criteria, and are enrolled will be followed during treatment and 6 months post-treatment. For most participants, this will be approximately 12 months after provisional enrollment/treatment start if they have drug-susceptible (DS) TB, and receive a standard 6-month TB regimen, but it may be longer if they have drug-resistant (DR) TB or require a longer treatment regimen for other reasons (e.g., toxicity, pregnancy). They will be requested to provide samples at 4-6 visits – Baseline, Visit 1, Visit 2, End of Treatment, and at

the time of suspected or confirmed treatment failure, TB relapse, or withdrawal (Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit). Samples will also be collected if TB relapse is suspected at the 6-Month Post-Treatment Visit or the participant reported having a relapse of TB. Participants may be called in between visits to remind them of upcoming study visits and standard of care visits.

If blood collection volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the ICMR or local IRB/IEC guidelines, specimens will be prioritized as outlined in the RePORT India Laboratory Manual. When respiratory samples are required from children 14 years of age or younger, nasopharyngeal (NP) aspirates or gastric aspirates (GAs) may be collected instead of sputum.

If the participant has not had a chest x-ray (CXR) as part of the clinical investigation of his/her TB through the usual diagnostic mechanisms, or as part of the CRU's Parent Protocol, a baseline CXR will be performed to characterize the extent of lung disease and identify the presence or absence of cavitation. Pregnant participants are not required to have a CXR. Participants 18 years of age or older and children born to an HIV-positive mother in Cohort A must provide documentation of HIV status or be willing to be tested for HIV, though they can participate regardless of the result. If the HIV test is positive, a CD4 count will be performed if not already available through the RNTCP within the preceding 6 months. Drug susceptibility testing (DST) will be performed as part of the study procedures but eligibility is not contingent on DST results.

3.2 Cohort A: Inclusion and Exclusion Criteria

It is very important that biological specimens be collected from individuals prior to, or very soon after initiation of standard rifampicin-based 6-month multidrug TB treatment, so that the full panoply of biological signals and signal modulation can be correlated with treatment response. Thus, individuals with suspected, but not yet confirmed active pulmonary TB (newly diagnosed or relapsed TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB) will be recruited into the study. If active pulmonary TB is not confirmed (see Section 4.2.3, Confirmatory Inclusion Criteria), individuals will subsequently be excluded from the active pulmonary TB cohort. Their specimens (or a subset) however, may be retained as control samples. There are no age restrictions for enrolment into the Common Protocol.

3.2.1 Provisional Inclusion Criteria

Individual recruiting CRUs may impose stricter screening criteria for their Parent Protocol in order to be consistent with local or national guidelines; but to be considered eligible for provisional enrolment in the Common Protocol, an individual suspected of having newly diagnosed TB or TB relapse, including MDR and XDR TB, must meet the following criteria:

1. Presents with one of the following:
    a. Presumed DS TB case: Signs or symptoms consistent with active pulmonary TB that include, but are not limited to: persistent cough, hemoptysis, fever, unintended weight loss or failure to thrive (children), fatigue or lethargy, night sweats, or pleuritic chest pain (see the MOP for definitions); or

b. Presumed MDR/XDR TB: Individuals already diagnosed with pulmonary TB, but not responding to treatment with first-line standard anti-TB drugs, e.g., persistent symptoms or persistently positive microbiology results, and are thus suspected to have MDR or XDR TB.

2. Has documentation of one of the following:
   a. CXR findings consistent with TB;
   b. Sputum smear-positive by microscopy; or
   c. Mtb detection by rapid diagnostic test, such as GeneXpert.
3. Has documentation of, or willingness to be tested for HIV infection. Adults (≥18 years of age) and children born to an HIV-positive mother must provide documentation of HIV status (confirmed positive test any time in the past or last negative test within 90 days prior to the Screening Visit) or be willing to be tested as part of the study.
4. Has provided written consent or witnessed oral consent in the case of illiteracy, prior to his/her first sample or other study-specific data being collected, or parents/legal guardians have provided consent for all minors and children have provided assent, as dictated by the CRU's IRB/IEC and country-specific regulations.
5. Agrees to the collection and storage of blood, urine, and sputum specimens for use for future research. (The participant may decline collection of specimens for human genetic research and still be eligible for the study.)

3.2.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the following criteria:

1. Plans to move from his/her current residence, which would interfere with the participant's ability to complete all study visits (through the 6-Month Post-Treatment Visit).
2. Has an active psychiatric condition, or alcohol or drug dependence that, in the opinion of the site investigator or designee, might interfere with the ability to give true informed consent and to adhere to the study requirements.
3. Is currently imprisoned.
4. Additional Exclusion Criteria for Presumed DS TB:
   a. Received >1 week (daily or intermittent doses) of any drugs with anti-TB activity within 30 days prior to provisional enrollment, including:
      i. First line anti-TB drugs in any combination: isoniazid (INH), rifampicin, pyrazinamide, ethambutol, and streptomycin;
      ii. Fluoroquinolones: e.g., ofloxacin, ciprofloxin, levofloxacin, moxifloxacin, nalidixic acid, sparfloxacin, and gatifloxacin;
      iii. Injectable second line anti-TB drugs: e.g., kanamycin, amikacin, and capreomycin;
      iv. Oral second line anti-TB drugs: e.g., p-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide, thiocetazone; or
      v. Other bacteriostatic second-line anti-TB drugs: e.g., clofazamine, linezolid amoxicillin/clavulanate, imipenem/cilastin, meropenam, clarithromycin, bedaquiline, and delamanid.

5. Additional Exclusion Criteria for Presumed MDR TB:
   a. Received >1 week (daily or intermittent doses) of drugs with anti-TB activity, other than first-line anti-TB drugs, within 30 days prior to provisional enrollment. These include:
      i. Fluoroquinolones: e.g., ofloxacin, ciprofloxin, levofloxacin, moxifloxacin, nalidixic acid, sparfloxacin, and gatifloxacin;
      ii. Injectable second line anti-TB drugs: e.g., kanamycin, amikacin, and capreomycin;
      iii. Oral second line anti-TB drugs: e.g., p-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide, thiocetazone; or
      iv. Other bacteriostatic second-line anti-TB drugs: e.g., clofazamine, linezolid amoxicillin/clavulanate, imipenem/cilastin, meropenam, clarithromycin, bedaquiline, and delamanid.
6. Additional Exclusion Criteria for Presumed Pre-XDR and XDR TB:
   a. Received >1 week (daily or intermittent doses) of current anti-Pre-XDR or XDR TB regimen within 30 days prior to provisional enrollment.

3.2.3 Confirmatory Inclusion Criteria

Due to delays associated with culture confirmation, full eligibility may not be determined immediately. Final confirmation must be documented within 6 months after provisional enrollment into the study. Provisionally enrolled participants must meet disease confirmation criteria to remain study-eligible, as defined below:

1. Culture-confirmed pulmonary TB (regardless of age or initial smear results):
   a. Mtb identified by culture of expectorated or induced sputum (a positive culture of NP aspirates or GAs may also be accepted in lieu of sputum culture for children ≤14 years of age).
   b. Mtb identified by culture results from respiratory secretions obtained by bronchoalveolar lavage or bronchial wash may not be used to determine study eligibility.
   c. Mtb identified from either liquid or solid culture is acceptable, and may be from either clinical or study-related specimens.
   d. Those who have extra-pulmonary manifestations of TB in addition to pulmonary TB may also be enrolled.
2. Clinically-documented pulmonary TB is allowed for children (≤14 years of age)[7, 8] who are culture-negative or culture-unknown and meet the following criteria[2]:
   a. Signs or symptoms consistent with TB;
   b. Culture-negative after two attempts at sputum collection using expectorated or induced sputum, NP aspirates, or GAs (or has documented reason for lack of specimen for culture);
   c. A CXR that is consistent with intrathoracic disease due to TB; and
   d. There is at least one of the following:
      i. A positive clinical response to standard multidrug anti-TB therapy;

ii. Documented exposure to a case of active TB (active TB case has documented or verbal report of smear-positive, culture-positive, or TB treatment); or

iii. Immunological evidence of Mtb infection (e.g., reactive tuberculin skin test [TST] or positive Interferon-Gamma Release Assay [IGRA]).

3. Additional Confirmatory Inclusion Criteria for MDR/XDR TB:
   a. DST or other appropriate molecular testing (see Laboratory Manual) to confirm MDR/XDR status*

   *MDR/XDR suspected participants who are not confirmed to have MDR or XDR TB may remain on study as long as all criteria for DS participants were met, otherwise, they will be discontinued from the study.

Participants who fail to meet the confirmatory inclusion criteria noted above will be discontinued from the study. However, specimens that were previously collected from the participant may be retained for use as control specimens.

3.3 Clinical and Laboratory Evaluations for Cohort A

The following clinical and laboratory evaluations will be performed on each participant, after signed informed consent is obtained or assent with parental/legal guardian consent is obtained. See Section 4.5, Schedule of Events for Cohort A – Active Pulmonary TB, for a tabulated summary of the evaluations described below. See the RePORT India Laboratory Manual for detailed instructions on specimen collection, prioritization, processing, storage, and shipping procedures.

3.3.1 Screening

Screening evaluations will be conducted to ensure that individuals meet eligibility criteria outlined in Section 4.2, Cohort A: Inclusion and Exclusion Criteria, prior to enrollment.

Each individual who is approached for study participation will be entered into the Screening and Enrollment Log (see the MOP for information about the log).

3.3.2 Baseline

Provisional eligibility will be verified before evaluations at the Baseline Visit are performed. Once baseline evaluations are conducted, the participant is considered provisionally enrolled in the study. The following evaluations will be performed or abstracted from the participant's medical chart or research record at the Baseline Visit:

1. Demographics, medical history, targeted concomitant medication history, and clinical data (see the MOP for a list of targeted concomitant medications)
2. Clinical evaluation
   a. A CXR, if not done as part of standard of care or as part of the Parent Protocol within 4 weeks prior to the Baseline Visit (not required for pregnant participants).
3. Local laboratory evaluations

   Data will be abstracted from the participant's medical chart or research record if tests below were performed as part of standard of care or as part of the Parent Protocol; otherwise, specimens will be collected (when applicable) and sent to the local laboratory for testing:

a. HIV test per the National AIDS Control Organization (NACO) guidelines (not required if there is documentation of a confirmed positive test at any time in the past; the last negative HIV test was obtained ≤90 days prior to the study visit; or the participant is a child <18 years of age who was not born to an HIV-positive mother; abstract the data from the participant's medical chart or research record).
b. CD4 count if HIV-infected
c. Complete blood count (CBC) and lymphocyte count
d. Hemoglobin A1c (HbA1c)
e. Sputum smear, culture, and DST (A specimen must be collected even if one was collected as part of standard of care just prior to enrollment.) The DST should be completed, as follows:
   i. DST for first-line anti-TB drugs for all participants.
   ii. DST for second-line anti-TB drugs if there is evidence of first-line drug-resistance.

4. Specimen collection for Central Biorepository storage

The following specimens will be collected for Central Biorepository storage. Refer to Section 6, Off-Study Criteria for Cohorts A and B, for the minimum specimen collection requirement at the Baseline Visit in order for participants to remain on study (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Mtb isolate subculture
b. Whole blood (PAXgene)
c. Whole blood (genetic analyses)
d. Whole blood (PBMC, plasma)
e. Urine
f. Sputum
g. Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

Note: If blood volume, in combination with other clinical or protocol blood volume requirements exceeds the allowable limit**, request the participant to return at the earliest possible time point to collect the baseline specimens.**

3.3.3 Visit 1

Visit 1 will be scheduled based on the participant's presumed drug resistance profile and length of treatment regimen, as follows:

Participant's Presumed/Confirmed Drug Resistance Profile	Length of Treatment	Timing of Visit 1 (Window)
DS TB	Not applicable	Week 4 (-1 wk/+3 wks)*
MDR TB	6-9 months	Week 4 (-1 wk/+3 wks)*
	>18 months	Week 12 (-1 wk/+4 wks)
XDR TB	Not applicable	Week 12 (-1wk/+4 wks)

***** When scheduling Visit 2 (Week 8), there must be a minimum of 3 weeks between Visit 1 and Visit 2.

If it is suspected that a participant has emerging resistance, evaluations for the TX F/R/W Visit will be conducted at this visit (see Section 4.3.7, Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit).

The following Visit 1 evaluations will be performed:

1. Medical history (participant status) since the previous visit:
   a. Eligibility confirmation when possible (see Section 4.2.3, Confirmatory Inclusion Criteria)
   b. TB treatment history (including clinical and laboratory evaluations)
   c. TB treatment adherence
   d. TB signs and symptoms
   e. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. Local laboratory evaluations
   a. Sputum smear and culture (when specimen can be obtained)
3. Specimen collection for Central Biorepository storage
   The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):
   a. Whole blood (PAXgene)
   b. Whole blood (PBMC, plasma)
   c. Urine
   d. Sputum

3.3.4 Visit 2

Visit 2 will be scheduled as follows:

Participant's Presumed/Confirmed Drug Resistance Profile	**Length of Treatment**	**Timing of Visit 2 (Window)**
DS TB	Not applicable	Week 8 (+4 weeks)*
MDR TB	6-9 months	Week 8 (+4 weeks)*
	>18 months	Week 24 (+/-4 weeks)
XDR TB	Not applicable	Week 24 (+/-4 weeks)

*****Visit 2 must be at least 3 weeks after Visit 1. For example, if Visit 1 was conducted 7 weeks after enrollment, visit 2 will be conducted between 10 and 12 weeks after enrollment.

If it is suspected that a participant has emerging resistance, evaluations for the TX F/R/W Visit will be conducted at this visit (see Section 4.3.7, TX F/R/W Visit).

The following Visit 2 evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. Eligibility confirmation when possible, if not done previously (see Section 4.2.3, Confirmatory Inclusion Criteria)
    b. TB treatment history (including clinical and laboratory evaluations)
    c. TB treatment adherence
    d. TB signs and symptoms
    e. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. Clinical evaluation
    a. CXR data will be collected if conducted as part of standard of care or as part of the Parent Protocol. A separate CXR will not be conducted for the Common Protocol.
3. Local laboratory evaluations
    a. Sputum smear and culture (when specimen can be obtained)
4. Specimen collection for Central Biorepository storage

    The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):
    a. Whole blood (PAXgene)
    b. Whole blood (genetic analyses)
    c. Whole blood (PBMC, plasma)
    d. Urine
    e. Sputum

3.3.5 End of Treatment (-4 Weeks/+6 Weeks)

The End of Treatment Visit will take place when the participant completes his/her prescribed TB treatment regimen. This will be at approximately 6 months for participants with DS TB on firstline multidrug TB therapy, and usually later for those with MDR or XDR TB. This visit may be conducted up to 4 weeks before or 6 weeks after the target visit date.

If it is suspected that a participant has treatment failure or TB relapse, evaluations for the TX F/R/W Visit will be conducted at this visit (see Section 4.3.7, TX F/R/W Visit).

The following End of TX evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. Eligibility confirmation, when possible, if not done previously (see Section 4.2.3, Confirmatory Inclusion Criteria)
    b. TB treatment history (including clinical and laboratory evaluations)
    c. TB treatment adherence
    d. TB signs and symptoms
    e. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. Clinical evaluation
    a. CXR data will be collected if conducted as part of standard of care or as part of the Parent Protocol. A separate CXR will not be conducted for the Common Protocol.

3. Local laboratory evaluations
    a. Sputum smear and culture (when specimen can be obtained)
4. Specimen collection for Central Biorepository storage

    The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

    a. Whole blood (PAXgene)
    b. Whole blood (genetic analyses)
    c. Whole blood (PBMC, plasma)
    d. Urine
    e. Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

3.3.6 6-Month Post-Treatment (-4 Weeks/+6 Weeks)

The final study visit will be conducted 6 months after the participant's prescribed TB treatment is completed either in-person or by phone. This visit may be conducted up to 4 weeks before or 6 weeks after the target visit date. The following evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. TB treatment history (including clinical and laboratory evaluations)
    b. TB treatment adherence
    c. TB signs and symptoms and determination of final outcome status
    d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)

If it is suspected that the participant has TB relapse, evaluations for the TX F/R/W Visit will be conducted (see Section 4.3.7, TX F/R/W Visit).

3.3.7 Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit

If a participant is suspected to have emerging resistance, treatment failure or TB relapse in between study visits, or met any other criteria for premature discontinuation (see Section 6, Off-Study Criteria for Cohorts A and B), the participant will be requested to come in for an inperson TX F/R/W Visit as soon as possible. If criteria for emerging resistance, treatment failure, or TB relapse are met, or the participant withdraws from the study for any reason, this will be the participant's final study visit.

The following evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. Eligibility confirmation, when possible, if not done previously (see Section 4.2.3, Confirmatory Inclusion Criteria)
    b. TB treatment history (including clinical and laboratory evaluations)
    c. TB treatment adherence
    d. TB signs and symptoms
    e. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. Clinical evaluation

a. Assess for treatment failure or TB relapse, to determine if bacteriologic or clinical outcome criteria have been met (see section 4.4, Outcome Measures for Cohort A).
b. CXR data will be collected if conducted as part of the standard of care or as part of the Parent Protocol. A separate CXR will not be conducted for the Common Protocol.

3. Local laboratory evaluations

Data will be abstracted from the participant's medical chart or research record if tests below were performed as part of standard of care or as part of the Parent Protocol. In addition to abstracting data, specimens will be collected for the following:

a. Smear and culture of sputum, or other site of active TB, and DST. The DST should be completed, as follows:
   i. DST for first-line anti-TB drugs for all participants.
   ii. DST for second-line anti-TB drugs if there is evidence of first-line drug-resistance.
b. HIV test (not required if there is documentation of a confirmed positive test at any time in the past; the last negative HIV test was obtained ≤90 days prior to the study visit; or the participant is a child <18 years of age who was not born to an HIVpositive mother; abstract the data from the participant's medical chart or research record)
c. CD4 count, only if HIV-infected (not required if collected as part of standard of care or as part of the Parent Protocol within the preceding 6 months; data will be abstracted from the participant's medical chart or research record)

4. Specimen collection for Central Biorepository storage

The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Mtb isolate subculture
b. Whole blood (PAXgene)
c. Whole blood (genetic analyses)
d. Whole blood (PBMC, plasma)
e. Urine
f. Sputum
g. Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

3.4 Outcome Measures for Cohort A

Data for Cohort A will be collected to support several key outcome measures as defined below:

1. Bacteriologic Outcomes for Participants who Initially have Bacteriologically-Confirmed, DS TB[5]

a. DS bacteriologic cure: Completion of standard, first-line multidrug TB therapy and the participant has documentation of a negative culture result in the last month of treatment and on at least one previous occasion.
b. DS treatment completed/bacteriologic status indeterminate: Completion of standard, first-line multidrug TB therapy without evidence of bacteriologic failure but without documentation of a negative culture result in the last month of treatment and on at least one previous occasion, either because tests were not done or because results are unavailable.
c. DS bacteriologic failure: A participant whose sputum culture is positive at Month 5 or later during treatment and the culture has not been determined to be a falsepositive culture.
d. DS bacteriologic relapse***:** Participant was declared *cured* or *treatment completed/bacteriologic status indeterminate* at the end of his/her most recent course of treatment, and is then diagnosed with a recurrent episode of TB confirmed by a clinical specimen collected from any anatomical site during the follow-up phase that is culture-positive for Mtb, when the culture has not been determined to be a false-positive culture.

   *The term "relapse" is used per the World Health Organization (WHO) definition. It is recognized that without genotype results, a status between relapse and **reinfection** cannot be discriminated.
e. DS emerging resistance**:** A participant who has a change in baseline drug sensitivity before DS bacteriologic failure can be determined (i.e., after the Baseline Visit, but before Month 5 of treatment).

2. Bacteriologic Outcomes for Participants who Initially have Bacteriologically-Confirmed, MDR or XDR TB
   a. DR bacteriologic cure: Completion of MDR or XDR TB treatment as recommended by National TB policy and 3 or more negative consecutive cultures taken at least 30 days apart after the intensive phase and no evidence of bacteriologic or clinical failure between the last negative culture and end of treatment.
   b. DR treatment completed/bacteriologic status indeterminate: Completion of MDR or XDR TB treatment, as recommended by National TB policy, without documentation of 3 or more negative consecutive cultures as defined under bacteriologic cure, but no evidence of bacteriologic or clinical failure.
   c. DR bacteriologic failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:
      i. Lack of culture conversion to negative status by the end of the intensive phase; or
      ii. Culture reversion to positive status in the continuation phase after conversion to negative during the intensive phase; or
      iii. Evidence of additional acquired drug-resistance to fluoroquinolones or secondline injectable drugs.

d. DR bacteriologic relapse*: Participants who were declared *cured* or *treatment completed* at the end of their most recent course of MDR or XDR treatment, and are then diagnosed with a recurrent episode of TB confirmed by a clinical specimen collected from any anatomical site during the follow-up phase that is culturepositive for Mtb, when the culture has not been determined to be a false-positive culture.
   *The term "relapse" is used per the WHO definition. It is recognized that without genotype results, a status between relapse and reinfection cannot be discriminated.

e. DR emerging resistance: A participant who has a change in baseline drug sensitivity before DR bacteriologic failure can be determined (i.e., after the Baseline Visit, but before the end of the intensive phase of treatment).

3. **Clinical Outcomes**

Note: Participants who achieve a bacteriologic outcome will not be assigned a clinical outcome.

Participants ≤14 years of age who did not have culture results or were culture-negative at the beginning will be assigned a clinical outcome. In addition, some adults or children with initial bacteriologically-confirmed TB may be assigned a clinical outcome (i.e., not bacteriologically-confirmed), as defined below. These outcomes are based on signs and symptoms of TB without accompanying bacteriologic confirmation.

a. **Clinical response:** Completion of TB treatment as recommended by National TB policy in a child participant ≤14 years of age who has resolution, by the end of therapy, of signs and symptoms attributable to TB. Participants older than 14 years of age cannot be assigned a clinical response outcome.

b. **Clinical failure:** A child with clinically documented TB or any participant with bacteriologically-confirmed TB may meet the definition for clinical (i.e., not cultureconfirmed) failure if he/she completes 4 full months of anti-TB treatment but remains ill with persistence, progression, or recurrence of signs or symptoms of TB that are determined to be due to TB and not due to another underlying cause.

c. **Clinical relapse*:** A child with clinically documented TB or any participant with bacteriologically-confirmed TB may meet the definition for clinical relapse (i.e., not culture-confirmed) if he/she meets the definition for clinical response or bacteriologic cure or treatment completed/bacteriologic status indeterminate, and
   is subsequently diagnosed with a recurrent episode of TB that is not confirmed by culture.
   *The term "relapse" is used per the WHO definition. It is recognized that without genotype results, a status between relapse and **reinfection** cannot be discriminated.

4. **Other Outcome Status Criteria**

These definitions apply to either DS or DR TB:

a. **Death:** A participant who dies for any reason after consenting to participate and prior to the end of study.

b. **Treatment incomplete:** A participant who drops out of treatment (defined as treatment interruption for 2 or more consecutive months), but continues in study follow-up.
c. **Lost to follow-up/unknown:** A participant who no longer participates in study visit follow-up or an outcome status cannot be determined.

5. **Completion of Therapy Status**

These definitions apply to either DS or DR TB:

a. **Completion of adequate therapy:** Considered accomplished when the participant is not a treatment failure, does not meet criteria for incomplete treatment, and has received at least 90% of the recommended number of doses of RNTCP-specified multidrug anti-TB therapy within 1 year of treatment initiation for DS participants and 2 years for MDR/XDR participants.
b. **Incomplete:** Treatment is considered incomplete if the participant has defaulted from treatment, defined as treatment interruption for 2 or more consecutive months.

3.5 Schedule of Events for Cohort A – Active Pulmonary TB

			TREATMENT PHASE				
Activities / **Visit**	**SCREENING**	**BASELINE**	**VISIT 1**	**VISIT 2**	**END OF TX (-4 wks/+6 wks**	**6-M POST-TX (-4 weeks/+6 wks)[h]**	**TX F/R/W**
Informed consent	X						
Eligibility assessment	X	X					
Eligibility confirmation[f]			**X**	**X**	**X**		**X**
Demographic, medical history, and clinical data		X					
Participant status[i]			X	X	X	X	X
CXR[a]		X		X[a]	X[a]		X[a]
HIV test[b]		X					X
CD4 count if HIV-infected[b]		X					X
CBC and lymphocyte count		X					
HbA1c		X					
Sputum smear & culture[c, d]		X	X	X	X		X
Sputum DST[c, d]		X					X
Mtb isolate subculture for storage		X					X
Whole blood (PAXgene) for storage		X[e]	X	X	X		X
Whole blood (PBMC **and plasma**) for storage		X[e]	X	X	X		X
Whole blood for storage (genetic analyses)		X[e]		**X**	**X**		**X**
Saliva for storage[g] (genetic analyses)		X			X		X
Urine for storage		X	X	X	X		X
Sputum for storage[d]		X	X	X			X

[a] CXR at baseline, unless done within 4 weeks prior to the Baseline Visit as part of standard of care or through the Parent Protocol. Data from Visit 2, End of Treatment, and TX F/R/W Visits will be collected if CXRs were conducted as part of standard of care or as part of the Parent Protocol. Pregnant women are not required to have a CXR.

[b] HIV testing to be performed per national guidelines. HIV testing not required if there is documentation of a confirmed positive test at any time in the past or the last negative HIV test was obtained ≤90 days prior to the study visit; or the participant is a child <18 years of age who was not born to an HIVpositive mother; abstract the data from the participant's medical chart or research record; CD4 count will only be performed on participants who are HIV-positive and who have not had a CD4 count performed in the preceding 6 months.

[c] For children whose diagnosis was made on the basis of an NP aspirate, GA, or clinical criteria, subsequent NP/GA inductions will not be required.

[d] Children diagnosed clinically and who are unable to expectorate will not be expected to provide these specimens.

[e] If blood volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the ICMR or IRB/IEC guidelines, the participant will be requested to return at the earliest possible time point to collect the baseline specimen, as long as the minimum specimen collection criterion is met before more than 1 week of anti-TB therapy was received (see protocol section 6).

[f] Eligibility confirmation, when possible, if not done previously.

[g] CRUs may choose not to collect saliva specimens for participants <5 years of age.

[h] If TB relapse is suspected at the 6-Month Post-Treatment Visit, complete evaluations required for the TX F/R/W Visit.

[i] Clinical assessment, as needed

4. Cohort B: Household Contacts at Risk for Progression to TB

4.1 Design and Procedures

The main goal of Cohort B is to identify HHCs of an infectious TB case at risk of progression to active TB over a 24-month time span. Participants being recruited in the context of a study developed and approved by the RePORT India Consortium (e.g., Parent Protocol), who are at risk for progression to active TB, will have the option of participating in the Common Protocol. Other HHCs referred to the CRU may also participate in the Common Protocol. Some individuals, namely young children and individuals with HIV infection, may be offered and prescribed isoniazid prophylaxis once identified as a contact of a case of active TB as part of standard of care. Individuals will be eligible for study entry regardless of their prophylaxis status, though information about their treatment will be collected.

Participants who voluntarily agree to take part will be required to sign a Common Protocol ICF before they can be screened for eligibility. Assent forms will be signed by children, as required by the local IRB/IEC, accompanied by an ICF signed by their parents/legal guardians (see Appendices C and D). Those that meet eligibility criteria and are enrolled will be followed for 24 months. Participants will be requested to give samples at the Baseline Visit. Additional samples will be collected if a participant develops active TB within the 24 months of follow-up, and the participant will be encouraged to enroll in Cohort A. Specimens from individuals who develop active TB will be saved over the life span of the biorepository. If blood volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the ICMR or local IRB/IEC guidelines, specimens will be prioritized as outlined in the Laboratory Manual.

4.2 Cohort B: Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

To be considered eligible for enrollment, an individual must meet the following criteria:

1. Is an adult or child with significant recent exposure (within the past 6 months) to an adult with untreated or inadequately treated pulmonary TB (see the MOP for detailed definitions).
2. Has no clinical signs or symptoms of active TB that include, but are not limited to: persistent cough, hemoptysis, fever, unintended weight loss or failure to thrive (children), fatigue or lethargy, night sweats, pleuritic chest pain, draining lymph node, or other evidence of extra-pulmonary TB. If clinical signs or symptoms of TB are present, CXR and/or sputum culture results must be included in the overall evaluation to rule out active TB.
3. Has provided written consent or witnessed oral consent in the case of illiteracy, prior to his/her first sample or other study-specific data being collected, or parents/legal guardians have provided consent for all minors and children have provided assent, as dictated by the CRU's IRB/IEC and country-specific regulations.
4. Agrees to the collection and storage of blood, urine, and sputum specimens for use for future research. (The participant may decline collection of specimens for human genetic research and still be eligible for the study)

4.2.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the following criteria:

1. Plans to move from his/her current residence, which would interfere with the participant's ability to complete all study visits (through the Month 24 Visit).
2. Has an active psychiatric condition, or alcohol or drug dependence that, in the opinion of the site investigator or designee, might interfere with the ability to give true informed consent and to adhere to the study requirements.
3. Is currently imprisoned.

4.3 Clinical and Laboratory Evaluations for Cohort B

The following clinical and laboratory evaluations will be performed on each participant, after signed informed consent is obtained or assent with parental/legal guardian consent is obtained. See Section 5.5, Schedule of Events for Cohort B – HHCs, for a tabulated summary of the evaluations described below. See the Laboratory Manual for detailed instructions on specimen collection, prioritization, processing, storage, and shipping procedures.

4.3.1 Screening

Screening evaluations will be conducted to ensure that individuals meet the eligibility criteria outlined in Section 5.2, Cohort B: Inclusion and Exclusion Criteria.

Each individual who is approached for study participation will be entered into the Screening and Enrollment Log (see the MOP for information about Screening and Enrollment Log).

4.3.2 Baseline

Eligibility must be verified before evaluations at the Baseline Visit are performed. Once baseline evaluations are conducted, the participant is considered enrolled in the study. The following evaluations will be performed or abstracted from the participant's medical chart or research record at the Baseline Visit:

1. Demographics, medical history, targeted concomitant medication history, and clinical data (see the MOP for a list of targeted concomitant medications)
2. TST or IGRA, if not completed as part of standard of care or as part of the Parent Protocol. Participants who are TST or IGRA negative will be asked to return to the clinic to re-assess their TST or IGRA status within 4 to 12 months after the Baseline Visit.
3. Specimen collection for Central Biorepository storage

   The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

   a. Whole blood (PAXgene)
   b. Whole blood (PBMC, plasma)
   c. Whole blood (IGRA)
   d. Whole blood (genetic analyses)
   e. Urine
   f. Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

   Note: If blood volume, in combination with other clinical or protocol blood volume requirements exceeds the allowable limit, request the participant to return at the earliest possible time point to collect the baseline specimens.

4.3.3 Month 4-6 Follow-Up Visit

Individuals who were TST or IGRA positive at baseline may have the Month 4-6 Follow-Up Visit conducted by phone. However, individuals who were TST or IGRA negative at baseline will be asked to return for a clinic visit to re-assess their TST or IGRA status. The following evaluations will be conducted:

1. Medical history (participant status)
   a. TB prophylaxis (e.g., INH or INH/rifampin) and TB treatment history
   b. TB signs and symptoms
   c. Abstraction of laboratory and/or CXR information, if done as part of standard of care or the Parent Protocol
   d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. If the Baseline Visit TST or IGRA result was negative:

a. Conduct a TST or IGRA. If a repeat test was performed between 6 weeks after the Baseline Visit and before the Month 4-6 Visit, a repeat test is not required. Result(s) may be abstracted from the participant's medical chart or research record. If the Parent Protocol conducts the repeat TST or IGRA test at Month 12 and not at the Month 4-6 Follow-Up Visit, the Parent Protocol schedule may be followed.

b. Specimen collection for Central Biorepository storage
The following Central Biorepository specimens will be collected (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

i. Whole blood (PAXgene)

ii. Whole blood (PBMC, plasma)

iii. Whole blood (IGRA)

iv. Whole blood (genetic analyses)

v. Urine

vi Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

4.3.4 Month 12 Follow-Up Visit (+/-2 Months)

Individuals who were TST or IGRA positive at baseline or had a repeat test at the Month 4-6 Visit may have the Month 12 Follow-up visit conducted by phone. However, individuals who were TST or IGRA negative at baseline and did not have a repeat test before the Month 12 visit will be asked to return for a clinic visit to re-assess their TST or IGRA status. The following evaluations will be conducted:

1. Medical history (participant status)
   a. TB prophylaxis (e.g., INH or INH/rifampin) and TB treatment history
   b. TB signs and symptoms
   c. Abstraction of laboratory and/or CXR information, if done as part of standard of care or the Parent Protocol
   d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. If the Baseline Visit TST or IGRA result was negative and a repeat test result was not documented prior to the Month 12 Visit:
   a. Conduct a TST or IGRA. If a repeat test was performed as part of standard of care or the Parent Protocol, result(s) may be abstracted from the participant's medical chart or research record.
   b. Specimen collection for Central Biorepository storage

   The following Central Biorepository specimens will be collected (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

   i. Whole blood (PAXgene)

   ii. Whole blood (PBMC, plasma)

iii. Whole blood (IGRA)
iv. Whole blood (genetic analyses)
v Urine
vi Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

4.3.5 Month 24 Follow-Up Visit (+/-2 Months)

The Month 24 Follow-up visit may be conducted by phone. The following evaluations will be conducted:

1. Medical history (participant status)
    a. TB prophylaxis (e.g., INH or INH/rifampin) and TB treatment history
    b. TB signs and symptoms
    c. Abstraction of laboratory and/or CXR information, if done as part of standard of care or the Parent Protocol
    d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
    e. Determination of final outcome status

4.3.6 TB Activation Evaluation Visit

If a participant is suspected to have active TB or has been confirmed to have active TB in between scheduled study visits, request the participant come in for an in-person TB Activation Evaluation Visit as soon as possible. If it is determined that a TB outcome measure has been met, this will be the participant's final study visit.

The following evaluations will be performed:

1. Medical history (participant status)
    a. TB prophylaxis (e.g., INH or INH/rifampin) and TB treatment history
    b. TB signs and symptoms
    c. Laboratory and/or CXR data will be abstracted, if done as part of standard of care or the Parent Protocol
    d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
2. Clinical evaluation
    a. Assess for active pulmonary and/or extra-pulmonary TB to determine whether or not a TB outcome has been met (see section 5.4, Outcome Measures for Cohort B)
    b. CXR if not done as part of standard of care or as part of the Parent Protocol (not required for pregnant participants)
3. Local laboratory evaluations

    Data will be abstracted from the participant's medical chart or research record if tests were performed as part of the standard of care or as part of the Parent Protocol. In addition to abstracting data, specimens will be collected for the following:

    a. Smear and culture of sputum, or other site of active TB, and DST. The DST should be completed as follows:

i DST for first-line anti-TB drugs for all participants.

ii DST for second-line anti-TB drugs if there is evidence of first-line drug-resistance.

b. HIV test (not required if there is documentation of a confirmed positive test at any time in the past; the last negative HIV test was obtained ≤90 days prior to the study visit; or the participant is a child <18 years of age who was not born to an HIV positive mother; abstract the data from the participant's medical chart or research record).
c. CD4 count if HIV-positive (not required if collected as part of standard of care or as part of the Parent Protocol within the preceding 6 months; data will be abstracted from the participant's medical chart or research record).
d. CBC and lymphocyte count (not required if collected within 4 weeks prior to the TB Activation Evaluation Visit as part of standard of care or as part of the Parent Protocol; data will be abstracted from the participant's medical chart or research record).
e. HbA1c (not required if collected within 4 weeks prior to the TB Activation Evaluation Visit as part of standard of care or as part of the Parent Protocol; data will be abstracted from the participant's medical chart or research record).

4. Specimen collection for Central Biorepository storage

The following specimens will be collected for Central Biorepository storage (see the Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Mtb isolate subculture
b. Whole blood (PAXgene)
c. Whole blood (PBMC, plasma)
d. Whole blood (IGRA)
e. Whole blood (genetic analyses)
f. Urine
g. Sputum
h. Saliva (genetic analyses): CRUs may choose not to collect saliva from children <5 years of age

4.3.7 Premature Discontinuation Visit

Participants who meet criteria for premature discontinuation other than TB activation (see Section 6, Off-Study Criteria for Cohorts A and B) should have a final study visit at the time it is decided to terminate study participation. The following evaluations will be performed:

1. Medical history (participant status)
   a. TB prophylaxis (e.g., INH or INH/rifampin) and TB treatment history
   b. TB signs and symptoms
   c. Abstraction of laboratory and/or CXR information, if done as part of standard of care or the Parent Protocol

d. Targeted concomitant medications (see the MOP for a list of targeted concomitant medications)
e. Determination of final outcome status

4.4 Outcome Measures for Cohort B

Case Definitions for Outcome Measures

Active TB is the outcome measure of interest in this cohort. All participants must be assigned only one outcome, as defined below:

1. **No TB:** Participant had no indication of active TB (pulmonary or extra-pulmonary) over the 24-month follow-up period.
2. **Definite case:** Culture-confirmed or GeneXpert-confirmed Mtb from any anatomical site over the 24-month follow-up period.
3. **Probable case (adult or child of any age):**
   a. Signs or symptoms consistent with active TB that include persistent cough, hemoptysis, fever, unintended weight loss or failure to thrive (children), fatigue or lethargy, night sweats, pleuritic chest pain, draining lymph node, or other evidence of extra-pulmonary TB (see the MOP for definitions); and
   b. Acid-fast bacilli (AFB) seen on microscopic examination of sputum or biopsy specimen, but without culture confirmation.
4. **Probable case (child ≤14 years of age[2]):**
   a. Signs or symptoms consistent with active TB that include persistent cough, hemoptysis, fever, unintended weight loss or failure to thrive (children), fatigue or lethargy, night sweats, pleuritic chest pain, draining lymph node, or other evidence of extra-pulmonary TB (see the MOP for definitions); and
   b. AFB smear and culture-negative, not done, or results unknown; and
   c. A CXR that is consistent with intrathoracic disease due to TB or radiographic or other evidence of extra-pulmonary TB; and
   d. There is at least one of the following:
      i. A positive clinical response to standard multidrug anti-TB treatment; ii. Documented exposure to a case of active TB; or iii. Immunological evidence of Mtb infection (e.g., reactive TST or positive IGRA).
5. **Possible case (adult or child of any age[2]):**
   a. Signs or symptoms consistent with active TB that include persistent cough, hemoptysis, fever, unintended weight loss or failure to thrive (children), fatigue or lethargy, night sweats, pleuritic chest pain, draining lymph node, or other evidence of extra-pulmonary TB (see the MOP for definitions); and
   b. AFB smear and culture-negative, not done, or results unknown; and
   c. There is at least one of the following:
      i. A CXR that is consistent with intrathoracic disease due to TB or radiographic or other evidence of extra-pulmonary TB; ii. A positive clinical response to standard multidrug anti-TB treatment; iii. Documented exposure to a case of active TB; or iv. Immunological evidence of Mtb infection (e.g., reactive TST or positive IGRA).

6. **Other Outcome Status Criteria**
   a. **Death:** A participant who dies for any reason after consenting to participate and prior to the end of study.
   b. **Lost to follow-up/unknown:** A participant who no longer participates in study visit follow-up or an outcome status cannot be determined.

4.5 Schedule of Events for Cohort B – Household Contacts

Activities / Visit	SCREENING	BASELINE	MONTH 4-6[e]	MONTH 12[e] (+/-2 months)	MONTH 24[e] (+/-2 months) and PREM DC	TB ACTIVATION EVALUATION
Informed consent	X					
Eligibility assessment	X	X				
Demographic, medical history, and clinical data		X				
IGRA or TST		**X**	**X**[j]	**X**[k]		
Participant status[f]			X[e]	X[e]	X[e]	X
Smear and culture from TB activation site[a]						X
Mtb isolate subculture for storage						X
Sputum DST[a]						X
Sputum for storage						X
Whole blood (PAXgene) for storage		**X**[i]	**X**[l]	**X**[l]		X
Whole blood (PBMC, **plasma**) for storage		**X**[i]	**X**[l]	**X**[l]		X
Whole blood (IGRA) for storage		X[i]	X[l]	X[l]		X
Whole blood (genetic analyses) for storage		**X**[i]	**X**[l]	**X**[l]		X
Saliva (genetic analyses)[g] for storage		X[i]	**X**[l]	**X**[l]		X
Urine for storage		X[i]	**X**[l]	**X**[l]		X
CXR[b]						X
HIV test if status is unknown[c]						X
CD4 count if HIV-infected[d]						X
CBC and lymphocyte count[h]						X
HbA1c[h]						X

[a] Smear and culture to determine participant's bacteriologic status. Speciation and drug sensitivity to be performed if TB is suspected. All those determined to have active TB will have all specimens saved in the biorepository and will be requested to roll over to Cohort A.

[b] CXR to rule out active TB unless one was taken as a part of standard of care or the Parent Protocol; pregnant women are not required to have a CXR. [c] HIV testing to be performed per national guidelines. HIV testing not required if there is documentation of a confirmed positive test at any time in the past or the last negative HIV test was obtained ≤90 days prior to the study visit; or the participant is a child <18 years of age who was not born to an HIV-positive mother; abstract the data from the participant's medical chart or research record. [d] CD4 count will only be performed on

participants who are HIV-positive and who have not had a CD4 count performed in the preceding 6 months as a part of standard of care or the Parent Protocol.

[e] Visits may take place via phone contact, unless a repeat TST or IGRA is needed or TB disease is suspected.

[f] Clinical assessment, as needed.

[g] CRUs may choose not to collect saliva specimens for participants <5 years of age.

[h] CBC, lymphocyte count, and HbA1c are not required if collected within 4 weeks prior to the TB Activation Evaluation Visit as part of standard of care or as part of the Parent Protocol.

[i] If blood volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the ICMR or IRB/IEC guidelines, request the participant to return at the earliest possible time point to collect the baseline specimen. [j] Month 4-6 Visit: Repeat TST or IGRA to be performed if baseline test was negative and a repeat test was not performed as part of standard of care or the Parent Protocol between 6 weeks after the Baseline Visit and before the Month 4-6 Visit. If the Parent Protocol conducts the repeat TST or IGRA test at Month 12 and not at the Month 4-6 Follow-Up Visit, the Parent Protocol schedule may be followed. [k] Month 12: Repeat TST or IGRA to be performed if baseline test was negative and a repeat test was not performed before the Month 12 Visit. [l] Months 4-6 and 12: Only collect biorepository specimens if a repeat TST or IGRA is being conducted for participants who had a negative baseline result or if the repeat test was conducted prior to the visit and Central Biorepository specimens were not collected for storage.

5. Off-Study Criteria for Cohorts A and B

1. Participants in Cohort A will be discontinued from the study for the following reasons:
    a. The following required baseline biorepository specimens are not collected:
        i. Sputum for culture and Mtb isolate; ii. Sputum for storage; iii. Whole blood (PAXgene); and iv. Urine
    b. More than 1 week of anti-TB therapy, listed under the applicable exclusion criteria (i.e., DS, MDR, and XDR), is received before the following required baseline laboratory specimens are collected (see Section 4.2.2, Exclusion Criteria):
        i. Sputum for culture and Mtb isolate; ii. Sputum for storage; iii. Whole blood (PAXgene); and iv. Urine
    c. The provisional pulmonary TB diagnosis is not confirmed as defined by the protocol (see Section 4.2.3, Confirmatory Inclusion Criteria);
    d. An HIV test was not completed within 7 weeks after enrollment;
    e. A study outcome occurred:
        i. Completion of the 6-Month Post-Treatment Visit.
        ii. Treatment failure (bacteriologic or clinical); iii. TB relapse (bacteriologic or clinical); or iv. Emerging resistance; the

participant may re-enroll into Cohort A as an MDR or XDR participant, if all eligibility criteria are met**.**

2. Participants in Cohort B will be discontinued from the study for the following reasons:
    a. A study outcome occurred:
        i. Completion of the Month 24 Visit; or
        ii. Active TB develops before the Month 24 Visit; the participant may enroll into Cohort A if all eligibility criteria are met.
3. Participants in Cohort A or Cohort B will be discontinued from the study for any of the following reasons:
    a. The participant/parent/legal guardian withdraws consent and/or assent;
    b. The participant is lost to follow-up or moves out of the area;
    c. The participant dies;
    d. The participant was inadvertently enrolled;
    e. The investigator determines that further participation would be detrimental to the health or well-being of the participant;
    f. The study is stopped by a funding organization or other government agency; or
    g. The study has to stop for other administrative reasons.

6. Sample Size

The primary objective of the study is to provide specimens to Indian biomarker researchers and their collaborators for investigations intending to lead to a better understanding of the prognosis of TB disease and the pathogenesis of progression from TB exposure to active disease. To address this primary objective, biospecimens will be stored in a Central Biorepository over time from two prospective, observational cohorts, one with participants who have active pulmonary TB (Cohort A) and the second with participants who are HHCs of an active TB case (Cohort B). A range of possible outcomes for use in research studies has already been described. In addition, general information will be collected on study participants, including demographic, medical history, clinical data, CBC and lymphocyte counts, HbA1c, HIV testing status, and for those that are determined to be HIV-positive at the time of specimen collection, their CD4 count will be obtained. This information will be used in descriptive analyses to characterize the overall study population represented in the biorepository, for describing the characteristics of participants

whose specimens are included in a specific research project, and for selecting subsets of study participants whose specimens are of interest for inclusion in certain targeted research studies.

Estimates of the treatment failure/TB relapse rate among active TB cases and the active TB infection rate among HHCs of active TB cases were culled from the literature. These rates were then applied to the total numbers of active pulmonary TB cases (n=1,700) and TB-exposed HHCs (n=5,100) expected to be enrolled into the five Parent Protocols combined, in an effort to come up with estimates for the numbers of treatment failures/TB relapses and active TB infections available for inclusion in the Common Protocol.

1. Cohort A (Active Pulmonary TB): Based on the rates from the literature, it is estimated that between 5% and 10% of treated TB cases will result in treatment failure or TB relapse.[3, 4] Thus, among the 1,700 active TB participants enrolled in the combined protocols, it is expected that between 85 and 170 TB relapses or treatment failures will occur, with 128 being an approximate midpoint estimate.
2. Cohort B (Household Contacts): Several studies have been conducted to assess TB incidence among contacts of adult PTB cases.[9-14] In a meta-analysis of 25 studies, Fox, et. al., found that among contacts of TB cases (HHCs, close and casual contacts), incidence of TB was highest in the first year (1.5/100 person-years (PYs), followed by a decline to about 0.5/100 PYs after three years of follow-up.[10] In a retrospective study, Moran-Mendoza, et. al., reported a TB incidence of 2.4/100 PYs in HHCs. TB incidence rose with increasing TST reactions from 0.25/100 PYs (TST of 0-4mm) to 3.3/100 PYs (TST $\geq$ 15mm).[12] Based on the literature a cumulative two-year TB incidence of 5% was assumed for Cohort B participants (n=5,100), with an approximate estimate of 255 participants progressing to active TB disease.

Table 7.1: Projections of Available TB Treatment Failures/TB Relapses and Active TB Disease Among Household Contacts of Active TB Cases

Participants Available for Enrollment in the RePORT India Common Protocol		
Individual CRU Parent Protocols	Active TB Cases	HHCs of Active TB Cases
Drs. Roy and Ellner	**750**	**1,020**
Drs. Valluri and Vankayalapati	--	**1,500**
Drs. Viswanathan and Kornfeld	**120**	--
Drs. Gupta, **Chandrasekaran (formerly Swaminathan)**, Mave, and Kadam	**650**	**2,580**
Drs. Christopher and Ramakrishnan	**180**	--
Total enrolled across study protocols	**1,700**	**5,100**
Projected Numbers Obtained Applying Rates Available from Different Sources		
	Failures/Relapses Among Active TB Cases	**Active TB Infections Among Contacts of Active TB Cases**
Estimated rate	5**.0**%-10**.0**%[3, 4]	**5.0%10, 15, 16**
Projected number	**85-170**	**255**

7. Participating Cohort Research Units

The study is multicentered. Participating CRUs are located in the following cities in India: Pune, Hyderabad, Chennai, Vellore, and Puducherry and may be expanded to other locations.

8. Data Collection

The protocol team is responsible for the development of case report forms (CRFs) needed to collect the information required to implement this protocol.

All participant-related study information will be identified through the PID on all CRFs. Names and other personal identifiers will not be used on any CRFs, study-specific laboratory specimens, clinical evaluations, or laboratory results. The CXR images will be maintained digitally and archived as part of the study database and may be used for future studies. The PID Logbook,

source documents, and CRFs should also be made available to authorized representatives from regulatory and funding organizations.

Study monitoring data, including information about eligibility, demographic data, and medical history will be collected on CRFs. The CRF completion and data submission instructions, quality assurance requirements, source documentation guidelines, storage requirements, and CRFs that can serve as source documents for the study are located in the MOP.

8.1 Central Coordinating and Data Management Center

A Data Management Center will provide centralized data management training to the CRUs and additional training as needed. See the MOP for detailed information on data management and the Data Management Center's roles and responsibilities.

9. Central Biorepository

The National Institute for Research in Tuberculosis (NIRT) in Chennai will be the Central Biorepository for the Common Protocol. NIRT will provide centralized training and laboratory support to the CRUs as needed.

10. Specimens for Long-Term Storage at the Central Biorepository

All processing and aliquoting of samples will take place in the CRU laboratory prior to sending samples to the Central Biorepository (see Table 11.1). Samples will then be shipped to the Central Biorepository where they will be curated, managed, and stored for up to 15 years after study completion. Samples will only be destroyed with written permission from the funding organizations and according to local regulatory guidelines.

Participants' samples will be saved in the Central Biorepository at least until the end of their follow-up period. Samples from those who do not experience the outcome of interest (treatment failure or TB relapse for Cohort A, and development of active TB for Cohort B) will be available to serve as controls for those who do experience the outcomes.

Specimens collected from participants who develop one of the outcomes of interest may be stored for up to 15 years after study completion. In addition, a subset of control specimens may also be stored for up to 15 years after study completion. The CRUs will be provided with sample collection kits. Details for the collection, prioritization, processing, storage, and shipping of samples collected as part of the Common Protocol are presented in the Laboratory Manual.

Table 11.1: Central Biorepository Study Specimen Collection and Storage Chart (Adults and Children)

Specimen Type[b]		**Adults and Children (≥5 years of age)**	**Children (<5 years of age)** [a]
Whole blood (PAXgene RNA)		2.5 mL	2.5 mL
Whole blood (IGRA)-Cohort B only		4 mL (1 mL/tube)	4 mL (1 mL/tube)
Whole blood (genetic analyses)		**3-6** mL (BD EDTA)	**3-6** mL (BD EDTA)
PBMC		**8-**10 mL (BD Heparin)	**4-**6 mL (BD Heparin)
Plasma		Harvested from BD Heparin (PBMC) tubes above	Harvested from BD Heparin (PBMC) tubes above
Saliva (genetic analyses)		6 mL	6 mL CRUs may choose not to collect saliva
Urine		Spot urine (10 mL)	Spot urine (10 mL)
Sputum		Whatever volume is possible to collect	Whatever volume is possible to collect
Extracted host RNA		Prepared from PAXgene tube	Prepared from PAXgene tube
Mtb isolate	**Cohort A**	Subculture of original Mtb isolate, and relapse or failure isolate	Subculture of original Mtb isolate, and relapse or failure isolate
	Cohort B	Subculture of confirmatory Mtb isolate from each participant who develops active TB	Subculture of confirmatory Mtb isolate from each participant who develops active TB

[a] Refer to weight chart for maximum blood volume collection limits in the Laboratory Manual. Indicated blood collection volumes are intended for children ≥5 kg (or 11 lbs).

- [b] Refer to the RePORT India Laboratory Manual for the prioritization of specimens, should blood collection requirements exceed the allowable volume by the ICMR or local IRB/IEC guidelines.

11. Ethical Conduct of the Study

All participating CRUs must be in compliance with U.S. and Indian regulations applicable to research involving human subjects, and in accordance with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and ICMR guidelines. Should U.S. and Indian regulations and guidelines differ, the more restrictive regulations and guidelines will apply.

This protocol, the ICFs and assent forms, and any subsequent modifications will be reviewed and approved by the IRB/IEC responsible for oversight of the protocol, including any national IRB/IEC, as required. Subsequent to the initial review and approval, the protocol will be reviewed in accordance with the IRB/IEC requirements. See the MOP for further details on the ethical conduct of the study.

11.1 Participant Information and Informed Consent

Only participants who give informed consent or assent, and whose parents/legal guardians of minors provide consent, per IRB/IEC requirements, will be enrolled in the protocol. Potential participants will have the requirements of the protocol explained to them and they will have the opportunity to discuss the protocol with the site investigator or designee before consent/assent is obtained. They will be assured that their decision to participate is voluntary and made completely without prejudice to their future care and treatment. Once the study team member is satisfied that the participant has understood the requirements of the protocol and the ICF/assent form, the participant will be asked to sign and date the ICF/assent form. The originals will be retained in the CRU's research file and a copy will be provided to the participant.

Participants may refuse to participate in this protocol or parents/legal guardians may refuse to allow their children to participate. If they decide to participate, they may change their minds and discontinue after the study has started without facing penalties or loss of benefits. This will be monitored continuously throughout the study period. If the participant decides to leave the study, he/she can notify the Principal Investigator (PI) or designee. If enrolled participants want to

withdraw their consent for long-term storage and possible future research testing of their biological samples, they can simply contact the PI or designee. The samples remaining in storage will be destroyed and documented in the laboratory management system. See the MOP for further details on consenting procedures.

Assent for Minors: Assent will be obtained for children as required by India-specific regulations and IRB/IEC policies. The study will be explained to children in age-appropriate language and they will be invited to participate. If the child agrees to enroll in this study, a signature or thumbprint will be obtained on the assent form, per IRB/IEC policies. An ICF will be signed by the parent/legal guardian. If either or both parties are illiterate, a witness will be present during the informed consent process and will sign the ICF. If the child refuses, then he/she will not be enrolled, even if the parent/legal guardian consents. See Appendices B and D for sample assent forms.

11.2 Confidentiality

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The data will be entered into a secure database. Only PIs and specific collaborators will have access to these data. Data may be reviewed by representatives of the IRB/IEC, funding organizations or their representatives, and by others tasked with duties of monitoring and quality assurance. Research and clinical information relating to participants may be shared with other researchers through lectures or publications, but the participants will not be identified by name. All specimens will be labelled with a PID with no identifying information. All ICFs, assent forms, and any other documents with participants' names or addresses will be stored separately and in secure facilities.

Study participants will have the right to withdraw their permission for further use of their samples at any time during and after the study. Specimens at the Central Biorepository will be labelled with a coded, unique identifier that will not contain identifying information. See the MOP for further details on participant confidentiality.

11.3 Study Discontinuation

The study may be discontinued at any time by the IRB/IEC, a government agency such as the DBT or NIH, or other funding organization.