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

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LIST OF ABBREVIATIONS AND ACRONYMS

AFB	Acid-Fast Bacilli
CBC	Complete Blood Count
CD4/8	Cluster of Differentiation 4/8
CRF	Case Report Form
CRU	Cohort Research Unit
CTB2	Consortium for Tuberculosis Biomarkers
CXR	Chest X-Ray
DAIDS	(United States) Division of AIDS
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)
Hgb	Hemoglobin
HHC	Household Contact
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
IRB	Institutional Review Board
LTBI	Latent Tuberculosis Infection
MDR/XDR	Multidrug-Resistant/Extensively Drug-Resistant
MOP	Manual of Operating Procedures
mRNA	Messenger Ribonucleic Acid
Mtb	Mycobacterium Tuberculosis
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
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
RePORT	Regional Prospective Observational Research for Tuberculosis
RNA	Ribonucleic Acid
SDMC	Statistical and Data Management Center
SOP	Standard Operating Procedure
TB	Tuberculosis
TST	Tuberculin Skin Test
TX	Treatment
TX F/R/W	Treatment Failure/Relapse/Withdrawal Evaluation

WHO	World Health Organization

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PROTOCOL SCHEMA

PURPOSE: The primary purpose of RePORT International is to provide a platform for coordinated global tuberculosis (TB) research by establishing a common set of standards and definitions that are utilized in the context of observational clinical research prospective to perform clinical TB research. This will enable future research studies to use pooled data and well-curated biological specimens for future analysis. The RePORT International Common Protocol, describes the populations and processes for collecting the specimens and data.

DESIGN: The RePORT International Common Protocol describes a prospective observational non-interventional study open to enrollment of individuals with active or TB or household contacts (HHCs) to an active case of TB. Participants will provide clinical data plus blood, sputum, urine and saliva for specifically-defined Common Protocol research purposes, at specific time points. Participants with active pulmonary TB (Cohort A) will be followed during the treatment period and for 6 months after, while participants who are household contacts (HHCs) to an active case of TB (Cohort B) will be followed for a total of 24 months. Biospecimens will be banked by the individual RePORT consortiain aliquots described by the RePORT International Laboratory Manual in preparation for future analysis.

POPULATION: The RePORT International Common Protocol does not restrict the age or gender of participants enrolled into either of the two observational cohorts: active pulmonary TB and HHCs. Participants may be co-enrolled in an affiliated study, or may be enrolled primarily into a Common Protocol stand-alone cohort.

STUDY SIZE: The RePORT International Common Protocol will guide establishment and ongoing enrollment of patients into multiple prospective cohorts across the globe, and funding to support these cohort from the NIH/NIAID/DAIDS and host countries appears secure for at least the next 3-5 years. The hope is that such cohorts will be successful and garner new or additional resources beyond that, such that participants continue to accrue and a robust collection of data and specimens from participants meeting main endpoints are collected. However, an exact sample size cannot be proposed at this time.

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

PRIMARY OBJECTIVE: To provide specimens and linked clinical data to 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 active disease. The intent is that data and specimens will be used by the individual RePORT consortia while also being prepared to share these both nationally and internationally, through agreements and understandings to be determined by the RePORT International Executive Committee (EC) and other governing bodies, as applicable.

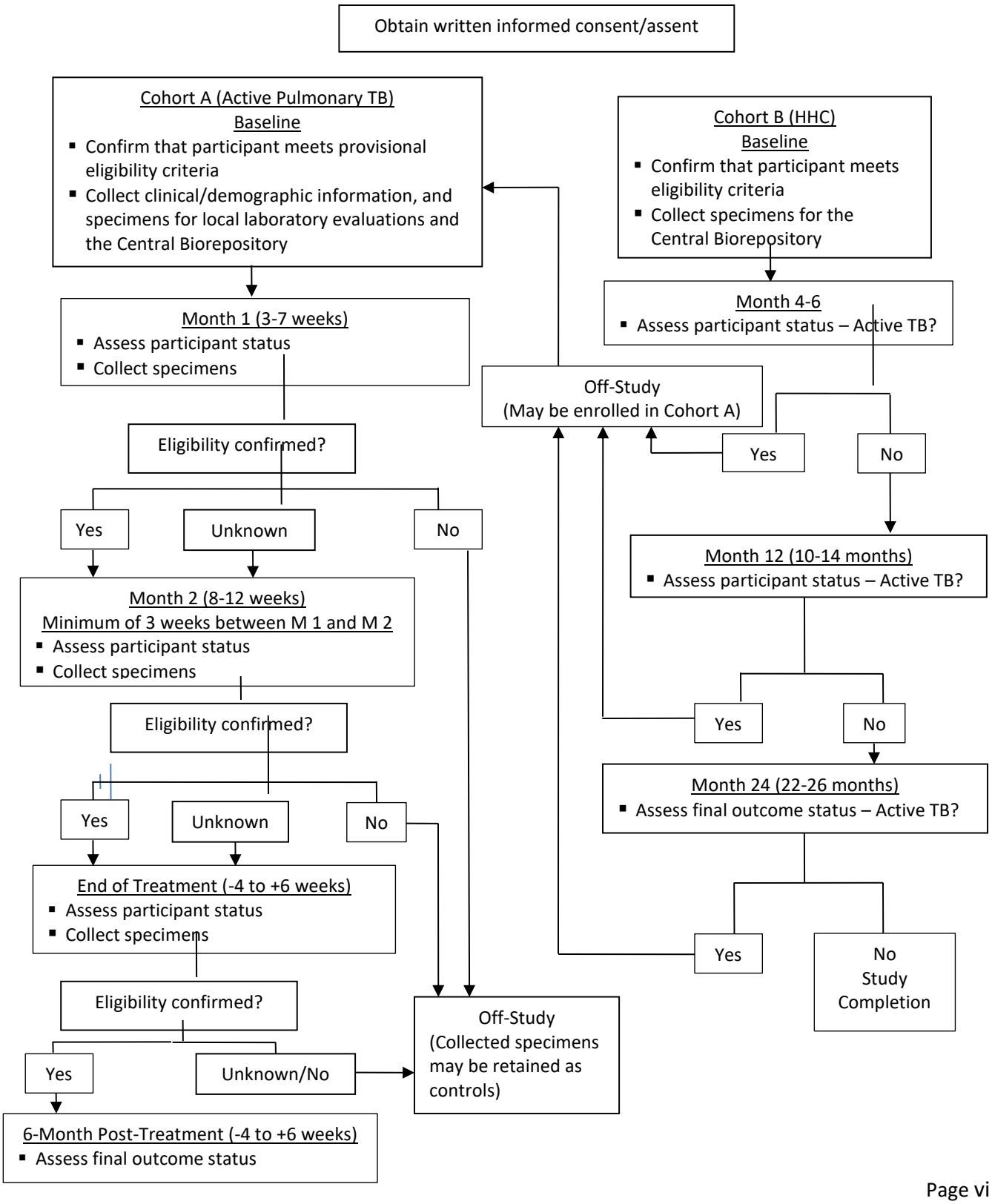
STUDY SITES: Currently, RePORT consortia have been established in India, Brazil, and Indonesia and will soon be established in South Africa. Data and bio-specimen repositories are being developed in each country to store their own data and samples. Each RePORT consortium is designed to support local, in-country TB-specific data, specimen bio-repositories, and associated research.

STATISTICAL AND DATA MANAGEMENT CENTER/ DATA MANAGEMENT CENTER: Each consortium will have its own Statistical and Data Management Center.

CENTRAL BIOREPOSITORY: Each consortium will have its own central biorespository.

U.S. COORDINATION SUPPORT CENTER: The RePORT International Coordination Center (RICC) is being established by NIH/DAIDS at FHI 360, to be led by Dr Carol Dukes Hamilton, with the purpose being to develop the mechanisms by which consortia can share data and specimens. The RICC will establish a RePORT International leadership and governance structure that will include regular reviews of data quality and completeness, update and distribute SOPs and MOPS, and insure cross-consortia harmonization. The RICC will also serve as the hub for data and specimen sharing requests and material transfer agreements (MTA) and will facilitate collaborative science include convening an annual scientific meeting.

PROTOCOL SCHEMA DIAGRAM



1. Background

Tuberculosis (TB) and HIV/AIDS are the two biggest causes of death among adults and pregnant women worldwide. 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 latent and active pulmonary TB participants. 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 "bank" 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 latent to active disease are needed to advance TB prevention efforts, both in vaccine development and treatment for prevention.

The U.S. National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) will co-fund host country or regional teams to perform individual cohort studies of active pulmonary and latent TB. The RePORT International Consortium presents a new and valuable opportunity to provide a platform for coordinated tuberculosis (TB) research by establishing a common set of standards and definitions to be utilized to perform clinical TB research. The Indo-US Vaccine Action Program, a collaboration between the Indian Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), and the US NIH, is co-funding five teams of India- and US-based investigators, to implement individual cohort studies of active and latent TB in India. In Brazil, the Brazilian Ministry of Heath, Department of Science and Technology (DECIT), and US NIH are co-funding a team of Brazil- and US based investigators

to enroll persons with active and latent TB. The US NIH and Indonesia NIH (Research and Development), will collaborate with the consortium through the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) project. This existing partnership between the two governments supports a network of nine academic and research institutions and hospitals to conduct research on infectious diseases and is currently conducting research on febrile illness in Indonesia. Additional networks are expected to be added, including a group in South Africa during 2016, helping to spur TB treatment and prevention research around the world.

The Common Protocol does not describe the specific research or analysis that will be done, and any future research will require a separate description and submission for ethical review.The intention, however, is that the informed consent process will be comprehensive enough to allow future research without the need for participant re-contact.

1.2 Study Objectives

The primary objective of the study is to provide specimens to RePORT consortia 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.

The intent is that data and specimens may be used by the individual RePORT consortia while also being harmonized for sharing both nationally and internationally, through agreements and understandings to be determined by a governing board of RePORT International.

1.3 Description of the Population

The Common Protocol will enroll participants with untreated active pulmonary TB (Cohort A) and those who were recently exposed to someone with active TB (Cohort B). The intention of this Common Protocol is to provide a mechanism by which each Cohort Research Unit (CRU) is responsible for collecting pre-determined clinical data and biological specimens at specified time points, using a unified protocol and standardized methods. The Common Protocol may be used as the primary, stand-alone mechanism for organizing a prospective, observational cohort, or may serve as a parallel or sub-study to an affiliated study, if the investigators deem it feasible. If the Common Protocol is conducted in conjunction with an affiliated study, when possible, Common Protocol 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.

Other TB trial organizations are also engaging in efforts to collect well-characterized TB specimens, which the RePORT consortia investigators may wish to collaborate with, such as the Consortium for TB Biomarkers (CTB2), http://www.tballiance.org/pipeline/innovation-detail.php?id=2. To the extent possible, the Common Protocol uses a similar standardized approach to specimen collection so that de-identified data, if not the samples themselves, might be correlated, pooled, and shared going forward.

2. Potential Risks and Benefits

Potential Known Risks

The risk for participating in the Common Protocol will be minimal and include additional blood, beyond what is collected for standard of care and the individual RePORT consortia parent protocol, if applicable for the biorepository, and any inconvenience for clinic and additional study visits described in the RePORT consortia parent protocol, if applicable There is a small risk of breach of confidentiality during this study; however, efforts directed to reduce this risk will be a priority. Each participant will be given a unique Participant Identification number (PID) and all data will be linked to this PID rather than by participant name or any other identifier. The TB infection status and other study data will be linked to the PID only.

Samples could be used for genetic analyses including genotyping. Samples will be archived, with informed consent from study participants, for future investigations of human host factors that are known to or may potentially influence TB treatment outcomes. In addition, other human genetic analyses related to HIV and other diseases may be performed. All of the genetic data and associated phenotypic/clinical data will be held in secure and confidential storage.

Potential Known Benefits

The long-term goal of this study is to provide clinical data and biological specimens that will lead to increased scientific evidence that can be translated into effective TB control. There may be no direct benefits to the participants. The positive impact of biomarkers on predicting TB outcomes, shortening product development timelines, or yielding effective prevention strategies may benefit future patients with TB. The data generated will be shared with the scientific community through scientific publications and presentations at scientific meetings.

3. Study Design

RePORT International consortia will enroll into one or both two prospective observational cohorts: one with participants who have active pulmonary TB (Cohort A) and the second with

participants who are an HHC to an active case of TB (Cohort B). The Common 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 individual RePORT consortia Central Biorepository. The resultant "bank" of biological samples will be made available to investigators participating in or collaborating with the RePORT consortia through a peer-review process that considers high-priority, credible proposals for their use. [*IF THE COMMON PROTOCOL WILL BE CONDUCTED IN CONJUNCTION WITH AN AFFILIATED STUDY, THEN THE FOLLOWING TEXT WILL BE INCLUDED:SAMPLES COLLECTED FOR EACH CRU'S AFFILIATED STUDY ARE TO BE KEPT SEPARATE FROM THE COMMON PROTOCOL SAMPLES, 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., chemokines, cytokines).
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 individual RePORT consortia, it is expected that the "bank" will also be available to investigators external to the RePORTconsortia, both nationally and internationally, if approved by the governing boards of the consortia 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 typical national TB program, Institutional

Review Board (IRB)/Independent Ethics Committee (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.

4. Cohort A: Participants with Active Pulmonary TB

4.1 Design and Procedures

Cohort A is a prospective observational non-interventional study open to enrollment for individuals with active pulmonary TB. TB clinical treatment will be managed by existing standard of care/systems, but those who provide informed consent and agree to participate will provide additional blood, sputum urine, and saliva Common Protocol research purposes, at specific time points. Participants may be co-enrolled in an affiliated observational or interventional study, or may be enrolled primarily into the Common Protocol as a stand-alone cohort.

Participants who voluntarily agree to take part will be required to sign a Common Protocol Informed Consent Form (ICF). The Informed consent process will be managed by research trained staff at each CRUs. 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 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, Month 1, Month 2, End of Treatment, and at the time of suspected or apparent treatment failure, TB relapse, or withdrawal (Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit). If TB relapse is suspected at the 6-Month Post-Treatment Visit or the participant reported having a relapse of TB, specimens will also be collected as required at the TX F/R/W Visit (see Section 4.5, Schedule of Events for Cohort A, Active Pulmonary TB).

If blood collection volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by RePORT International Manual of Operation (MOP) or local IRB/IEC guidelines, specimens will be prioritized as outlined in the RePORT International Laboratory Manual. When respiratory samples are required from children 10 years

of age or younger, nasopharyngeal (NP) aspirates or gastric aspirates (GAs) may be collected instead of sputum. Samples will also be collected if: 1) treatment failure or TB relapse is suspected/confirmed and evaluated at a TX F/R/W Visit; or 2) the participant voluntarily withdraws from the study prior to the 6-Month Post-Treatment Visit, at which point his/her final study outcome status will be determined (see Section 4.4, Outcome Measures for Cohort A).

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 RePORT consortia parent protocol procedures,if applicable, , 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 results. If the HIV test is positive, a CD4 count will be performed if not already available through standard of care or as part of the RePORT consortia parent protocol, if applicable 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.

4.2 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 presumptive, but not yet confirmed active pulmonary TB (newly diagnosed or TB relapse) 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 enrollment into the Common Protocol.

4.2.1 Provisional Inclusion Criteria

Individual RePORT consortia recruiting CRUs may impose stricter screening criteria in order to be consistent with local or national guidelines, but to be considered eligible for provisional enrollment in the Common Protocol, an individual with presumptive newly diagnosed TB or TB relapse (see Section 4.4, Outcome Measures for Cohort A for the definition of TB relapse) must meet the following criteria:

1. Presents with 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).

2. Has either CXR findings consistent with TB, and/or are sputum smear positive by microscopy or 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 (last negative test ≤90 days earlier) or be willing to be tested as part of the study. HIV testing does not need to be repeated if there is written documentation of a confirmed positive test at any time in the past.

4. Has signed a 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 consent by parents/legal guardians for all minors and assent from children, as dictated by the CRU's IRB/IEC and country-specific regulations.

5. Agrees to the collection and storage of blood, urine, saliva, 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. Received >1 week (daily or intermittent doses) of any drugs with anti-TB activity within 30 days prior to provisional enrollment, including:

    a. Any drug or combination of drugs typically used in a multidrug anti-TB therapy (isoniazid [INH], rifampicin, pyrazinamide, ethambutol*)*;

    b. Any fluoroquinolone (e.g., ofloxacin, ciprofloxin, levofloxacin, moxifloxacin, nalidixic acid, sparfloxacin, and gatifloxacin);

    c. Any other drugs with anti-TB activity (e.g., clofazamine, aminoglycosides [amikacin, kanamycin], or capreomycin).

2. 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).

3. 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.

4. Is currently imprisoned.

4.2.3 Confirmatory Inclusion Criteria

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

a. Adults must have pulmonary disease confired by culture.

i. 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 ≤10 years of age).

ii. Mtb identified by culture results from respiratory secretions obtained by bronchoalveolar lavage or bronchial wash **may not** be used to determine study eligibility.

iii. Mtb identified from either liquid or solid culture is acceptable, and may be from either clinical or study-related specimens.

iv. Those who have extra-pulmonary manifestations of TB in addition to pulmonary TB may also be enrolled.

Clinically-documented pulmonary TB is allowed for children (≤10 years of age)[7,8] who are culture-negative or culture-unknown and meet all the following criteria[1]:

i. Signs or symptoms consistent with TB (see Section 4.2.1, Provisional Inclusion Criteria 1);

ii. 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);

iii. A CXR that is consistent with intrathoracic disease due to TB; and

iv. There is at least one of the following:

- A positive clinical response to standard multidrug anti-TB therapy;
- Documented exposure to a case of active TB (active TB case has documented or verbal report of smear positive, culture positive, or TB treatment[2]);
- Immunological evidence of Mtb infection (e.g., reactive tuberculin skin test [TST] or positive Interferon-Gamma Release Assay [IGRA]).

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.

4.3 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 and their schedule of completion. See the RePORT International Laboratory Manual for detailed instructions on specimen collection, prioritization, processing, storage, and shipping.

4.3.1 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).

4.3.2 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 at the Baseline Visit:

1. Demographics, medical history, and clinical data
2. Clinical evaluation

a. A CXR, if not done as part of standard of care or as part of the RePORT consortia parent protocol, if applicable within 4 weeks prior to the Baseline Visit (not required for pregnant participants).

3. Local laboratory evaluations

Abstract data 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 RePORT consortia parent protocol, if applicable otherwise collect specimens (when applicable) and send them to the local laboratory for testing:

a. HIV test per the RePORT consortia national guidelines (if required; see Section 4.2.1, Provisional Inclusion Criteria)

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.) The DST should be completed, as follows:

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

ii. Conduct the 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 RePORT International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Mtb isolate subculture

b. Whole blood (PAXgene, IGRA, genetic analyses)

c. Whole blood (PBMC, plasma)

d. Urine

e. Sputum

f. Saliva (genetic analyses): Individual RePORT consortia 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, a specimen for genotyping may be collected at any other visit through the End of Treatment or TX F/R/W Visit.

4.3.3 Month 1 (Weeks 3-7)

The Month 1 Visit may be conducted any time between 3 and 7 weeks after enrollment. When scheduling the Month 2 Visit, there must be a minimum of 3 weeks between the visits.

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 evaluations will be performed:

1. Medical history (participant status)

    a. Eligibility confirmation when possible (see Section 4.2.3, Confirmatory Inclusion Criteria)

        b. TB treatment history

        c. TB treatment adherence

        d. TB signs and symptoms

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 Report International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Whole blood (PAXgene, IGRA)

b. Whole blood (PBMC, plasma)

c. Urine

d. Sputum

4.3.4 Month 2 (Weeks 8-12)

The Month 2 Visit may be conducted any time between 8 and 12 weeks after enrollment and must be at least 3 weeks after the Month 1 Visit. For example, if the Month 1 Visit was conducted 7 weeks after enrollment, the Month 2 Visit 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, Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit).

The following evaluations will be performed:

1. Medical history (participant status)
    a. Eligibility confirmation when possible, if not done previously (see Section 4.2.3, Confirmatory Inclusion Criteria)
    b. TB treatment history
    c. TB treatment adherence
    d. TB signs and symptoms
2. Clinical evaluation
    a. CXR data will be collected if conducted as part of standard of care or as part of the RePORT consortia parent protocol, if applicable. 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 Report International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Whole blood (PAXgene, IGRA)

b. Whole blood (PBMC, plasma)

c. Urine

d. Sputum

4.3.5 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 first-line multidrug TB therapy, and usually later for those with multidrug-resistant (MDR) or extensively drug-resistant (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, Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit).

The following evaluations will be performed:

1. Medical history (participant status)

a. Eligibility confirmation when possible, if not done previously (see Section 4.2.3, Confirmatory Inclusion Criteria)

b. TB treatment history

c. TB treatment adherence

d. TB signs and symptoms

2. Clinical evaluation

a. CXR data will be collected if conducted as part of standard of care or as part of the RePORT consortia parent protocol, if applicable.. 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 RePORT International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

a. Whole blood (PAXgene, IGRA)

b. Whole blood (PBMC, plasma)

c. Urine

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

4.3.6 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)

    a. TB treatment history

    b. TB treatment adherence

    c. TB signs and symptoms and determination of final outcome status

If at this final visit 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, Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit).

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

If a participant is suspected to have or has experienced 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), or are withdrawing from the study for any reason, request the participant to come in for an in-person TX F/R/W Visit as soon as possible.

The following evaluations will be performed:

1. Medical history (participant status)
    a. TB treatment history
    b. TB treatment adherence
    c. History of TB signs and symptoms

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)
    b. CXR data will be collected if conducted as part of standard of care or as part of the RePORT consortia parent protocol, if applicable. A separate CXR will not be conducted for the Common Protocol.

3. Specimen collection for Central Biorepository storage

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

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

4. Local laboratory evaluations

Abstract data from the participant's medical chart or research record if tests below were performed as part of standard of care or RePORT consortia parent protocol, if applicable In addition to abstracting the data, collect the following:

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

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

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

If the participant has met criteria for bacteriologic or clinical treatment failure or TB relapse, complete the following:

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-infected (not required if collected as part of standard of care or as part of the RePORT consortia parent protocol, if applicable within the preceding 6 months; abstract the data from the participant's medical chart or research record)

If results are pending and a determination of bacteriologic or clinical treatment failure or TB relapse cannot be made, the HIV test and CD4 count need not be completed. Later, if it is determined that these outcome criteria for treatment failure or TB relapse are met, request the participant to return to the clinic to complete the HIV test and CD4 count as soon as possible.

If it has been determined that a treatment failure or TB relapse outcome measure has been met, this will be the participant's final study visit.

4.4 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 false-positive 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 recurrence 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

three 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 second-line 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 culture-positive 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 recurrence 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 ≤10 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 ≤10 years of age who has resolution, by the end of therapy, of signs and symptoms attributable to TB. Participants older than 10 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 culture-confirmed) 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 recurrence 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, per individual RePORT consortia national guidelines, of multidrug anti-TB therapy within 1 year of treatment initiation for DS participants and within 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.

4.5 Schedule of Events for Cohort A - Active Pulmonary TB

	Treatment Phase						
Activities							
Visit	**SCREENING**	**BASELINE**	**MONTH 1 (weeks 3-7)**	**MONTH 2 (weeks 8-12)**	**End of TX (4 wks to +6 wks)**	**6-M POST-TX (4 weeks to +6 wks)[h]**	**TX F/R/W**
Informed consent	X						
Eligibility assessment	X	X					
Demographic, medical history, and clinical data		X					
Participant status			X	X	X	X	X
CXR[a]		X		X[a]	X[a]		X[a]
HIV test[b]		X					X[f]
CD4 count if HIV-infected[b]		X					X[f]
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	X	X	X		X
Whole blood (PBMC) for storage		X	X	X	X		X
Whole blood (IGRA) for storage		X	X	X	X		X
Plasma for storage		X	X	X	X		X
Whole blood for storage (genetic analyses)		X[e]					
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 as part of the Report consortia parent protocol if applicable Data from Month 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 or as part of the Report consortia parent protocol if applicable Pregnant women are not required to have a CXR.

[b] HIV testing on participants not known to be positive to be performed per national guidelines; 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 RePORT consortia national or applicable guidelines, or IRB/IEC guidelines, a specimen may be collected at any time during study follow-up through the End of Treatment or TX F/R/W Visits.

[f] Only required if bacteriologically or clinically confirmed to have treatment failure or TB relapse.

[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.

5. Cohort B: Participants who are Household contacts (HHC) to Active Cases of TB

5.1 Design and Procedures

Participants who are at high risk for progression to active TB will be recruited to participate in the Common Protocol. In particular, recent HHCs of an infectious case of TB will be recruited. The main goal of Cohort B will be to identify individuals who progress from latent to active TB over a 24-month time span. 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.

Specimens from individuals who progress to active TB will be saved over the life span of the biorepository. Participants who voluntarily agree to take part will be required to sign a Common Protocol ICF. 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 sign the ICF/Assent Form 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. If blood volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by RePORT consortia country's specific guidelines, as applicable, or local IRB/IEC guidelines, specimens will be prioritized as outlined in the RePORT International Laboratory Manual.

5.2 Cohort B: Inclusion and Exclusion Criteria

5.2.1 Inclusion Criteria

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

1. 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. 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 signed a 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 consent by parents/legal guardians for all minors and assent from children, 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.)

5. Agrees to either TST or IGRA laboratory test.

5.2.2 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.

5.3 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 for a tabulated summary of the evaluations described below and their schedule of completion. See the RePORT International Laboratory Manual for detailed instructions on specimen collection, prioritization, processing, storage, and shipping.

5.3.1 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).

5.3.2 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, and clinical data
2. IGRA or TST by Mantoux method using an approved Tuberculin/PPD product (e.g., Tuberculin-RT 23 SSI), if not completed as part of standard of care, to determine if there is immunologic evidence of latent TB infection (LTBI). **Note: HHCs may be enrolled whether or not there is evidence of LTBI**
3. Specimen collection for TST/IGRA testing and Central Biorepository storage

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

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

5.3.3 Follow-Up Visits Months 4-6, 12, and 24

Follow-up visits may be conducted by phone or in-person. The Month 12 Visit may be conducted between 10 and 14 months, and the Month 24 Visit may be conducted between 22 and 26 months after enrollment. 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 RePORT consortia parent common, if applicable.

d. Determination of final outcome status at Month 24

5.3.4 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 to come in for an in-person TB Activation Evaluation Visit as soon as possible.

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. History of TB signs and symptoms
2. Abstraction of laboratory and/or CXR information, if done as part of standard of care or RePORT consortia parent common, if applicable.
3. Clinical evaluation
    a. Assess for active pulmonary and/or extrapulmonary TB to determine whether or not a TB outcome has been met (see section 5.4)
    b. CXR if not done as part of standard of care or RePORT consortia parent common, if applicable. (not required for pregnant participants)
4. Specimen collection for Central Biorepository storage

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

a. Mtb isolate subculture

b. Whole blood (PAXgene, IGRA, genetic analyses)

c. Whole blood (PBMC, plasma)

d. Urine

e. Sputum

5. Local laboratory evaluations

Abstract data from the participant's medical chart or research record if tests were performed as part of the standard of care or as part of or RePORT consortia parent common, if applicable. In addition, conduct the following:

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

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

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

If participant has met criteria for definite TB, probable TB, or possible TB complete the following:

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-infected (not required if collected as part of standard of care or RePORT consortia parent common, if applicable within the preceding 6 months; abstract the data 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 or RePORT consortia parent common, if applicable. abstract the data 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 RePORT consortia parent common, if applicable; abstract the data from the participant's medical chart or research record).

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

If results are pending and a determination of definite, probable, or possible TB cannot be made, specimens for laboratory tests b-f will not be collected. Later, if it is determined that these outcome criteria are met, request the participant to return to the clinic to collect these specimens as soon as possible.

If it has been determined that a TB outcome measure has been met, this will be the participant's final study visit.

5.3.6 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. History of TB signs and symptoms
    c. Abstraction of laboratory and/or CXR information, if done as part of standard of care or RePORT consortia parent common, if applicable.
    d. Determination of final outcome status

5.4 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 ≤10 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 extrapulmonary 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. Chest radiography that is consistent with intrathoracic disease due to TB or radiographic or other evidence of extrapulmonary 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.

5.5 Schedule of Events for Cohort B - Household Contacts (HHC) to Active Cases of TB.

vities **Visit**	**SCREEING**	**BASELINE**	**MONTH 4-6**	**MONTH 12 (MONTHS 10-14)**	**MONTH 24 (MONTHS 22-26) and Prem DC**	**B ACTIVATION Evaluation**
Informed consent	X					
Eligibility assessment	X	X				
Demographic, medical history, and clinical data		X				
Participant status			X[e]	X[e]	X[e]	X
TST/IGRA		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				X
Whole blood (PBMC) for storage		X				X
Whole blood (IGRA) for storage		X				X
Whole blood for storage (genetic analyses)[i]						X
Saliva for storage (genetic analyses)[f, g]		X				X
Plasma for storage		X				X
Urine for storage		X				X
CXR[b]						X
HIV test if status is unknown[c, f]						X
CD4 count if HIV-infected[d, f]						X
CBC and lymphocyte count[f, h]						X
HbA1c[f, 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 RePORT consortia parent common, if applicable; pregnant women are not required to have a CXR.

[c] HIV testing to be performed per national guidelines. If documented positive status has been previously confirmed, no further testing is required.

[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 RePORT consortia parent common, if applicable.

[e] Participant status determination may take place via phone contact or in-person.

[f] Required at the TB Activation Evaluation Visit only if confirmed to have definite, probable, or possible TB.

[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 RePORT consortia parent common, if applicable.

[i] Exclude from collection if blood volume in combination with other clinical or protocol blood collection requirements exceed the allowable volume by RePORT consortia country's spefic guidelines, if applicable, or IRB/IEC guidelines

6. Off-Study Criteria for Cohorts A and B

1. Participants in Cohort A will be discontinued from the study for the following reasons:

    a. More than 1 week of anti-TB therapy was received before the following minimum required baseline laboratory specimens were collected:

        i. Sputum for culture and Mtb isolate;

        ii. Sputum for storage;

        iii. Blood for PBMCs and plasma; and

        iv. Urine

    b. The provisional pulmonary TB diagnosis is not confirmed as defined by the protocol (see Section 4.2.3, Confirmatory Inclusion Criteria);

    c. An HIV test was not completed within the Month 1 Visit window;

    d. A study outcome occurred:

        i. Treatment failure (bacteriologic or clinical);

        ii. TB relapse (bacteriologic or clinical);

        iii. Emerging resistance; or

        iv. Completion of the 6-Month Post-Treatment Visit.

2. Participants in Cohort B will be discontinued from the study for the following reasons:

    a. A study outcome occurred:

        i. Active TB develops before the Month 24 Visit; the participant may enroll into Cohort A if all eligibility criteria are met; or

        ii. Completion of the Month 24 Visit.

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.

7. Sample Size

The primary objective of the study is to provide specimens to 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 "banked" 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 case of TB (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 main endpoints – treatment failure/TB relapse rate among active TB cases and the progression to active TB among HHCs of active TB cases – were culled from the literature. These rates were then applied to a theoretical population (estimates of recruitment from the RePORT India cohort) of active pulmonary TB cases (n=5,500) and TB-exposed/HHCs (n=14,020). These scenarios are presented below:

1. Cohort A (Active Pulmonary TB): Based on the rates from the literature [I will give you a reference you can quote here], it is estimated that between 5% and 10% of treated TB cases will result in treatment failure or TB relapse. Thus, if 5,500 active TB participants are enrolled, it is expected that between 275 and 550 treatment failures or TB relapses

will occur, with 400 being an approximate midpoint estimate.

2. Cohort B (HHC): The rates reported in the Marais paper (see Table 7.1 below) indicate that the likelihood of progression from LTBI to active disease among individuals not receiving preventive treatment varies significantly by age. Furthermore, routine administration of preventive therapy is very uncommon in most high-burden settings. Thus, estimations are dependent on the proportion of children enrolled in the studies. Applying age-specific rates to the theoretical population of 14,020 HHC participants yields a wide range for the possible total number of participants that may develop active TB during study follow-up: 1298-2569. Assuming the approximate midpoint of this range, it appears that there could be about 1900 developing active TB if 14,020 HHCs were enrolled.
3. Table 7.1: Projections of Available TB Treatment Failures/TB Relapses and Active TB Infections Among Household Contacts (HHCs) of Active TB Cases

Estimated Enrollment in the RePORT India Common Protocol		
	Active TB Cases	HHCs of Active TB Cases
Estimated enrollment across RePORT India CRUs	5500	14020
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 Projected number	5%-10%[3,4] 275-550	2%-20%[5,6] 1298-2569*

* The estimated total number of active TB cases among HHCs was determined based on the population distribution given in the Roy, Ravikumar, Ellner RePORT India Parent Protocol, to which the age-specific rates given by Marais[6] were subsequently applied. See Table 7.2: Estimated Number of Active TB Cases Among HHCs of Active TB Cases by Age

Age	Estimated Distribution	Estimated Total Number	Estimated TB Case Rate	Estimated Total Number TB Cases
5-10 years	9.3%	1304	2%	26
>10 years	90.7%	12716	10%-20%	1272-2543
Totals		14020		1298-2569

Furthermore, based on multiple TB treatment and prevention trials, we know that the majority of disease failures and relapses will occur within 6 months of treatment completion, and thus we anticipate detecting >90% of all relapses by following the cohort for this time period . Similarly, we know from the literature that the highest risk time period for progression from recent TB infection to active TB disease is in the first 2 years after exposures. Thus, we anticipate the 24 month follow-up will allow us to detect >90% of all cases of LTBI that progress to active TB leading to between 1350 and 3000 events among the theoretical Indian consortium enrollees.

8. Participating Cohort Research Units

Currently, RePORT consortia have been established in India, Brazil, and Indonesia and discussions are underway in South Africa as well. Each reflects national research goals, but are coordinated through utilization of common standards and practices that are delineated by the RePORT International Common Protocol with corresponding case report forms and manual of operations. Data and bio-specimen repositories are being developed in each country to store their own data and samples. This platform sets the stage for future combined or comparative data analyses, and should be an invaluable resource for in-country and cross-national collaborations between bench and clinical researchers.

8.1 INDIVIDUAL COUNTRY COHORTS

RePORT INDIA

Investigators are funded directly by NIH and co-funded by the Governement of India to enroll subjects into their own parent protocol. Eligible subjects from each parent protocol will be asked to co-enroll into the RePORT International Common Protocol. All subjects will be enrolled from the sites in India, and are expected to enroll up to 5,500 active TB cases and 14,000 households contacts of active TB cases in their parent protocols. The sites are all experienced in TB clinical

research, represent a mix of urban and rural, geographically disparate populations, and bring unique interests and expertise to their parent projects. The specific sites comprising RePORT India include the M.V. Diabetes Research Centre (MVDRC) in Chennai, working with US partners at the University of Massachusetts to study the impact of diabetes on TB severity among adults; Byramjee Jeejeebhoy Medical College (BJMC) in Pune and the National Institute for Research in Tuberculosis (NIRT) in Chennai, working with US partners at Johns Hopkins University to investigate host and microbial factors associated with active and latent TB infection in adults and children; Blue Peter Public Health & Research (LEPRA) in Hyderabad, working with the University of Texas Health Science Center to study the role of cellular immunity in preventing progression to active TB; Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER) in Puducherry, working with Boston University Medical Center to study risk factors for treatment relapse and progression to active TB; and Christian Medical College (CMC) in Vellore, working with University of Washington to study the impact of adjunctive steroids for TB meningitis.

RePORT BRAZIL

Investigators are funded directly by NIH and co-funded by the Governement of Brazil and will be enrolling into a single protocol which is harmonized with the RePORT International Common Protocol. Four sites in Rio de Janeiro, one in Manaus, and one in Salvador were selected to enroll up to 900 active TB cases and 2700 close contacts of those TB cases. Vanderbilt University is the US-based academic partner working with RePORT Brazil. Sites will recruit sputum culture positive adults to observe the outcome of TB patients as well as the occurrence of TB among contacts with and without evidence of LTBI. Persons with LTBI will be offered isoniazid per Brazilian guidelines, while those who are Tuberculin Skin Testing (TST) or Interferon-gamma release assay (IGRA) negative will not receive treatment. The RePORT Brazil bio-repository will be in Salvador at the Instituto Brasileiro de Reabilitação (IBR).

RePORT INDONESIA

The Indonesia network is being funded directly by NIH and co-funded by the Governement of Indonesia has developed a study that will enroll 1000 presumptive new TB cases and 357 previously treated cases. Like RePORT Brazil, the parent study has been harmonized with RePORT International Common Protocol to harmonize collection of data and bio-specimens using standardized methods and agreed upon time points. Drug susceptible and multi drug resistant patients will be followed from commencement to end of treatment for drug sensitive patients and two years for MDR patients. Indonesia is considering expanding the study to include household contacts of active cases.

RePORT SOUTH AFRICA

RePORT consortia establishment discussions are underway in South Africa and will be funded directly by NIH and co-funded by the Governement of the Republic of South Africa

9. RePORT International Coordinating Center (RICC) and Participating Cohort Research Units (CRUs)

The purpose of RePORT International is to facilitate future combined or comparative analyses, and to be an invaluable resource for in-country and cross-national collaborations between bench and clinical researchers. The RICC is being established by NIH/DAIDS at FHI 360, to be led by Dr Carol Dukes Hamilton, with the purpose being to develop the mechanisms by which consortia can share data and specimens. The RICC will establish a RePORT International leadership and governance structure that will include regular reviews of data quality and completeness, update and distribute SOPs and MOPS, and insure cross-consortia harmonization. The RICC will also serve as the hub for data and specimen sharing requests and material transfer agreements (MTA) and will facilitate collaborative science include convening an annual scientific meeting.

The RICC will work closely with Westat, the NIH/DAIDS-funded CRSS contract monitoring organization, to provide feedback on the quality of data and specimens Each CRU will be expected to organize a research team that has the education and experience to fill key roles that include, at a minimum, a Site PI, Study Coordinator, and individuals responsible for Quality Assurance, Data Management and a Laboratory sample/Biorepository Manager. The Laboratory/Biorepository Manager will work closely with the local laboratory for initial specimen processing, as well as with Central Biorepository personnel to ensure safe and transport of specimens between the site and the Biorepository.

9. Data Collection

Each site is expected to have a trained Data Manager to oversee procedures included in the MOP in section 9.1. RePORT International has developed a set of case report forms (CRFs) that all RePORT International consortia are to use with as little modification as possible. Each RePORT consortia is expected to collect and store the information required to implement the Common Protocol according to detailed specifications designed to facilitate future data sharing. A Data Elements Bank has been developed in spreadsheet format that accompanies each CRF. The Data Bank lists all of the questions asked on the CRFs for the Common Protocol in the order they are asked. In addition to the attributes of long and short name, type, format, and permissible

outcomes for each question, the Data Bank has a tag that specifies which questions can and cannot be modified. Data delivered by the RePORT consortia will be evaluated against the Data Bank for adherence to the requirements of data collection.

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.

9.1 Statistical and Data Management Center

Statistical and Data Management Centers (SDMCs) will be located in the individual RePORT consortia. The SDMC will provide centralized data management training to the CRUs and additional training as needed. Detailed information on Data management, roles and responsibilities will be listed in the MOP. The RICC will establish a RePORT International leadership and governance structure that will include regular reviews of data quality and completeness, update and distribute SOPs and MOPS, and insure cross-consortia harmonization.

10. Central Biorepository

The central biorespository will be located in the country or region in which each RePORT consortium resides. The RICC will establish a RePORT International leadership and governance structure that will include regular reviews of laboratory SOPs and distribution of SOPs and MOPS, and insure cross-consortia harmonization. The RICC will also serve as the hub for data and specimen sharing requests and material transfer agreements (MTA) and will facilitate collaborative science include convening an annual scientific meeting. The RePORT Laboratory Manual will provide detailed guidelines for establishment and maintenance of the biorepository.

10.1 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. Each site is expected to provide a private place, appropriate to the site context, in order to protect confidentiality. 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.

11. 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 RePORT International Laboratory Manual.

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

Specimen Type	Adults and Children (≥5 years of age)	Children (<5 years of age)[a]

Whole blood[b] (PAXgene RNA)		2.5 mL	2.5 mL
Whole blood[b] (IGRA)		3 mL (1 mL/tube)	3 mL (1 mL/tube)
Whole blood (genetic analyses)		4 mL (BD EDTA)	4 mL[b] (BD EDTA)
PBMC		10 mL (BD Heparin)	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 RePORT International Laboratory Manual. Indicated blood collection volumes are intended for children ≥5 kg (or 11 lbs.).

[b] Exclude from collection if combined study and biobank blood volume limit is exceeded. See the RePORT International Laboratory Manual for maximum blood volume collection limits.

12. Ethical Conduct of the Study

All participating CRUs must be in compliance with U.S., national and local regulations and guidelines applicable to research involving human subjects, and in accordance with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP). Should regulations and guidelines differ between countries, 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.

12.1 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 individual RePORT consortia host country 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 fingerprint 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 consents. See Appendices B and D for sample assent forms.

12.2 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.

12.3 Study Discontinuation

The study may be discontinued at any time by the IRB/IEC, a government agency such as the RePORT International government funding agency or NIH, or other national agencies that have regulatory oversight.

13. Data Dissemination Plan and Publications

Any publications stemming from the development of a concept proposal using samples and data collected from this protocol will follow the individual RePORT consortia host country **[**Publication Guidelines maintained in the host country.

14. Biohazard Containment

As the transmission of pathogens can occur through contact with contaminated needles, blood, blood products, sputum, and saliva, appropriate blood and secretion precautions will be employed by all personnel in the collection of blood, sputum, and saliva specimens and shipping and handling of all specimens for this study, in accordance with institutional and national policies and regulations.

15. Quality Assurance and Cohort Research Unit Support Visits

The study will be conducted in compliance with the protocol, MOP, RePORT International Standard Operating Procedures (SOPs), GCP/Good Clinical Laboratory Practice (GCLP), and applicable regulatory requirements in RePORT consortia host country. Before implementation, the protocol and all relevant study documents, including recruiting materials, will be approved by the local IRBs/IECs and copies will be submitted to the RICC for reference. The accurate recording of data, record keeping, and archiving of essential documents will be the responsibility of each site within each consortium, but will

be remotely queried during periodic data reviews organized by the RICC to evaluate for quality and completeness of data collection.

The funding agency for the US component of RePORT International (NIH/DAIDS) provides individual and consortium-specific site support and quality assurance through the CRSS contract mechanism, currently led by Westat. They will perform periodic site visits to ensure protocol compliance, including the satisfactory completion of informed consent procedures, eligibility verification, source documentation collection and maintenance, and CRF completion, as needed. Investigators are required to make all study documents and pertinent records available for inspection by the staff conducting a site visit. The RICC will record the names and contact information of the person(s) at each CRU who is responsible for regular study monitoring, as well as identification, mitigation, reporting, and documentation of protocol violations and/or social harms.

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APPENDIX A: SAMPLE INFORMED CONSENT FORM ACTIVE PULMONARY TB (COHORT A)

For the protocol: "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM"
(RePORT INTERNATIONAL COMMON PROTOCOL)

BACKGROUND INFORMATION

NOTE: If you are a parent or legal guardian of a child participant "you" refers to "your child" throughout this document.

You have been invited to join this research study because you may have active tuberculosis (TB) of the lungs. Researchers are trying to learn more about TB. Much of TB research is done using human samples, such as blood, sputum (the mucous that you cough up), saliva (spit), and urine (pee). We are asking you to let us store some of your samples and your health information in a **"biobank"** and database so they might be used in future research studies. By using your samples and health information, researchers hope to find new ways to find, treat, and cure TB and also to prevent TB. Some of these studies may lead to new drugs, vaccines, or tests for TB. These future studies will include genetic and nongenetic studies. Genetic studies focus on your genes. Genes are your body's instructions to make and operate your body. Some studies may see how certain genes affect a person's ability to fight TB, or how a person responds to TB treatment. Future genetic studies on your samples will be related to TB and possibly other diseases (for example, HIV infection or diabetes) that may affect the course of TB in a person. We are not planning to do any tests that would affect how a doctor treats you or anybody in your family. These results will only be used for research.

WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this study is to create a "biobank," which is a collection of body samples from many people. These specimens are stored in a laboratory. Only researchers and staff working on the study, or who have special permission, will have access to (be able to use) the samples in the biobank. We are creating this biobank so a researcher can use the specimens to study TB or other diseases that may affect TB now or in the future.

A researcher's study must be approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). These committees help make sure your rights are protected and that you are safe. If the IRB/IEC approves the study, then the researcher may be given permission to use the specimens. The biobank will not give the researcher any information that could identify you like your name or address.

You will not be told the results of the tests conducted on the specimens in the biobank, because they will be done in the future and are not used for clinical care.

You have the choice to take part in this research study, or not. This Informed Consent Form (ICF) gives information to help you decide. Please read it carefully and take all the time you need to make your choice. Be sure to ask us as many questions as you want. Everyone who takes part in this research should know that:

- Taking part may involve some risks, but these risks are minimal.
- Taking part is voluntary. If you choose to participate and then later want to stop, you can quit at any time.
- No matter what you decide, now or in the future, it will not affect your medical care.

HOW MANY PEOPLE WILL BE ENROLLED INTO THIS RESEACH STUDY?

We plan to enroll approximately [*EACH REPORT CONSORTIA WILL FILL IN THEIR ENROLLMENT TARGETS FOR COHORT A*] people with active TB of the lungs and over *EACH REPORT CONSORTIA WILL FILL IN THEIR ENROLLMENT TARGETS FOR COHORT B*]people who live with or have been close to someone with active TB of the lungs.

HOW LONG WILL I BE IN THE STUDY?

How long you will be in the study depends on how long you have to take your TB medicines. Your last study visit will be 6 months after you finish your full course of TB medicines. For example, if you are on TB medicines for 6 months, your last visit will be about 1 year after you join the study (6 months after you finish your TB medicines). If you are on TB medicines for 1 year, then your last visit will be about 1 year and 6 months after you join the study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide that you would like to be in this study, we will ask you to sign this ICF. We will offer you a signed copy to keep. Here is what will happen next:

We will ask you some questions to make sure you are eligible to be in this study. If you are eligible and you decide to join this research study, you will be seen in the clinic 4 times – at Entry, Month 1, Month 2, and at the end of your TB treatment, which is usually about 6 months after you join the study, but could be longer. Your final visit, which will be about 6 months after you finish your treatment, will be done in the clinic or by phone to check your health status. ***IF THERE THERE WILL BE AN AFFILIATED STUDY, THE FOLLOWING TEXT WILL BE INCLUDED AS APPLICABLE: THESE VISITS [CRU TO ENTER APPLICABLE COMMON PROTOCOL STUDY VISITS] MAY BE ON THE SAME DAY AS THE [CRU TO ENTER AFFILIATED STUDY NAME, AS UNDERSTOOD BY THE PARTICIPANT] VISITS***]. We will review any medical information done as part of your regular care, such as chest x-rays, HIV tests, and TB testing done on your sputum. You may be asked to come in for a visit at other times if your TB

treatment is not working; or if after you complete your TB treatment period you get sick with TB again. If you decide you don't want to be in the study anymore, we will ask you to come in once more for a final visit. In addition, if the research staff finds out that you actually don't have TB (by looking at the result of one of the tests that will be done), you will be asked not to come for any more visits, but any collected specimens will remain in the biobank.

After you have read and signed this ICF, the following evaluations will be done in the clinic:

1. Before the Entry Visit

   The following will be done to make sure you are eligible to be in the study:

   a. Medical History and Current Health Status Reviews: We will review information about your medical history, including your TB history; check whether or not you have signs or symptoms of TB; and ask what medications you have taken or are taking right now. We will also review information about blood test results if you have HIV. If you do not have HIV or you don't know if you have HIV, and you are 18 years of age or older, or you are a child born to an HIV-positive mother, and have not been tested in the last 90 days, we will ask that you be tested.

2. Entry Visit:

   If you are eligible, and you want to be in the study, you will be enrolled by having an Entry Visit. This may happen today or you may return on another day. We will ask you some questions about yourself. We will also ask you for some contact information so we can remind you about your visits or check to see how you are doing. In addition, the following evaluations will be done:

   a. Medical History and Current Health Status Reviews: We will ask you questions about your TB signs and symptoms; if you have started taking TB medications, we will check your TB Treatment Card; and we may review your medical information related to TB, such as chest x-ray results, or laboratory results, or ask questions about previous illnesses you might have had.

   b. Sputum Collection: This will be for checking to make sure you have TB and to see which medicines might work and might not work. We will also send a specimen for storage in the biobank. If you have a hard time coughing up sputum, you may be asked to breathe in a steam-like mist through a mask. This mist will help you cough deeply. Some children may require a gastric aspirate (stomach sample). This will help the doctor know whether or not TB is making your child sick. This involves putting a small flexible tube in the nose and down to the stomach to get a specimen to test for TB.

   c. Blood Collection: This will be for storage in the biobank, including a sample to look at your genes, your body's instructions to make and operate your body. We will also check to see if you have anemia, diabetes, and other diseases, such as HIV if not already done as part of your medical care. If you are HIV-positive, an additional test called a CD4 count may be done to check your immune

status, which can tell us how well your body can fight infections. HIV counseling will also be provided. We will collect up to about 31.5 mLs (a little over 6 teaspoons) or 15.5 mLs (a little over 3 teaspoons) **[CRU TO MODIFY CHILD VOLUME TO INCLUDE HIV, CD4, CBC, HBA1C]**, if your child is less than 5 years of age.

d. Saliva (Spit) Collection: This will be for storage in the biobank to look at your genes. We will collect about 6 mLs (about 1 teaspoon). **[CRU TO ADD TEXT IF SAMPLES WILL NOT BE COLLECTED FROM CHILDREN LESS THAN 5 YEARS OF AGE.]**

e. Urine Collection: This will be for storage in the biobank. We will collect about 10 mLs (2 teaspoons) of urine.

f. Chest X-Ray: This will be done if one was not done as part of your regular medical care **[RePORT consortia *CRU TO ENTER OR AFFILIATED STUDY NAME, IF APPLICABLE*]**. We will keep a copy of your chest x-ray as part of your study records and it may also be used in future studies.

3. Follow-Up Visits: Month 1, Month 2, End of Treatment

The following evaluations will be done:

a. Medical History and Current Health Status Reviews: We will ask you questions about your TB signs and symptoms, check your TB Treatment Card to see if you have missed any TB medicines, and we may review your medical information if you had a regular medical visit since your last visit.

b. Sputum Collection: This will be used for checking your TB status (a smear and culture). Sputum will also be collected for storage in the biobank at the Month 1 and Month 2 Visits.

c. Blood Collection: This will be used for storage in the biobank. We will collect about 15.5 mLs (a little over 3 teaspoons) or 11.5 mLs (a little over 2 teaspoons) if your child is less than 5 years of age.

d. Saliva (Spit) Collection: This will be for storage in the biobank to look at your genes. We will collect about 6 mLs (about 1 teaspoon) at the End of Treatment Visit. **[RePORT consortia CRU TO ADD TEXT IF SAMPLES WILL NOT BE COLLECTED FROM CHILDREN LESS THAN 5 YEARS OF AGE.]**

e. Urine Collection: This will be used for storage in the biobank. We will collect about 10 mLs (2 teaspoons) of urine.

f. Chest X-Ray: At Month 2 and the End of Treatment Visits, results of your chest x-rays will be collected, if done as part of your regular medical care. You will not have a chest x-ray for this study at these visits. We will keep a copy of your chest x-ray as part of your study records and it may also be used in future studies.

4. Treatment Failure/Relapse/Withdrawal Evaluation Visit:

If you are not getting better, or after you finish your TB treatment you get sick again, or if you decide you want to come off the study for any reason, you will return for an extra visit as soon as possible. You will have most of the same evaluations you had at the Entry Visit.

If you want to stop being in the study or we find out that the medicines are not working or your TB came back this will be your final visit.

WHAT ARE THE POSSIBLE RISKS?

The samples being taken for biobank storage may be taken during routine medical care and procedures. There is minimal risk to you if you decide to participate in this study. The following describes some of the possible risks:

- Drawing blood may cause some discomfort, bleeding, and/or bruising where the needle enters the skin. In rare cases, there may be fainting or infection.
- The IRB/IEC only allows a certain amount of blood to be drawn in 1 day for your safety. We will only take an amount that is allowed by the IRB/IEC.
- There are no risks with coughing up sputum or breathing steam-like mist to help with deep coughing.
- A gastric aspiration (getting a stomach sample) is a simple procedure that involves putting a small flexible tube down your child's nose. This may cause some discomfort and/or cause your child to gag.
- Chest x-rays are done as part of routine medical care. The amount of radiation emitted during a chest x-ray is small and poses no significant risks to you. If you are pregnant, you will not be required to have a chest x-ray.
- There is a small risk that someone may use your health information and data from the study without proper permission. This incorrect use of information may cause discrimination, distress, or other problems to you. In order to reduce this risk, your name or any personal information will not be written on the research records; all records will be placed in locked cabinets in locked rooms. Only people working on the study, or who have special permission, will be able to see your information, including the information in the database in the computer.

WHERE WILL THE SAMPLES AND INFORMATION BE STORED?

Researchers will store your samples at the local clinical research site and then ship them to the RePORT consortia biobank. There is a possibility that researchers may send the samples to other researchers in your country or outside of your country.

Researchers will store your study information electronically in computer databases.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to us and we will make every effort to protect it. Here are just a few of the steps we will take:

- Only study code numbers will be used on your samples and study information. Your identity will not be known by the researchers who study your samples and health information. Published results will not include your private information.
- We will keep the list that links the code number to your name separate from the samples and information. Only certain research staff can see or use this list. We will keep the samples in locked freezers in locked buildings. We will keep health information and research information on secure computers. These computers have many levels of protection.
- An IRB/IEC will review and approve the research done on the samples collected for storage at the biobank.

WHO WILL SEE MY PRIVATE INFORMATION?

Apart from the research staff, representatives from the IRBs/IECs, funding organizations, and regulatory agencies may request to see your private information. In addition, your private information may be provided to national authorities as required by law

HOW LONG WILL RESEARCHERS STORE MY SAMPLES?

Researchers will store your samples for up to 15 years after study completion. However, you can change your mind and withdraw your permission to store them at any time.

WHAT ARE THE POSSIBLE BENEFITS?

This study will not help you directly; however, you will receive clinical laboratory test results that may give you and your doctor more information about your health (for example, complete blood count). The main reason you may want to take part is to help researchers make discoveries that might help you and other people now and in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you. You **[RePORT consortia *CRU TO MODIFY: WILL/WILL NOT*]** be paid **[*CRU TO INCLUDE COMPENSATION THAT WILL BE PROVIDED, IF APPLICABLE*]**. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits. If you experience injury as part of this research study, **[RePORT consortia *CRUS TO ADD WHAT CARE IS TO BE PROVIDED, PER IRB/IEC REQUIREMENTS*]**.

WHAT ARE MY OPTIONS?

Taking part in this study is your choice. You can choose to take part or not to take part. If you choose to take part, you can change your mind at any time.

WILL I BE TOLD IF THERE ARE NEW FINDINGS?

You will be given clinical laboratory test results that are done for this study. These results may give you and your doctor information about your health, specifically about TB, anemia, diabetes, and HIV.

You will not get test results from the samples that are collected for the biobank. These samples will be used by researchers in the future; and therefore, we will not have any test results to share with you. If you are interested in learning whether or not there are new findings in the future, you may contact **[*ENTER NAME OF CONTACT PERSON*] at [*TELEPHONE NUMBER*]**.

WHAT IF I CHANGE MY MIND?

You can decide to withdraw your permission whenever you want. If you decide to withdraw your permission, contact the research staff. There are two ways to withdraw your permission. You could allow researchers to remove all your personal identifiers linked to your stored samples, so that they are not linked to you anymore. These samples will then become anonymous. Or, you can ask researchers to destroy the samples. However, in either case, researchers will not be able to destroy samples or information from research that is already underway. If some tests have already been completed on your samples, any remaining samples will be destroyed. If you withdraw your permission, there will be no negative effects for you.

WHY WOULD THE RESEARCH DOCTOR TAKE ME OFF THIS RESEARCH STUDY?

The research doctor may need to take you off the study early without your permission if the study is cancelled by the funding organization(s) or by the IRB/IEC. The research doctor may also take you off early if your treatment does not work, you get TB again after you finish your treatment, or you are not able to attend the visits as required by the research study. Another reason the doctor may take you off this research study is if you develop other health problems that will make you unable to participate.

WHAT ARE MY RIGHTS AND WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

It is your right to decide if researchers can collect, store, and use your samples and information for research purposes. It is also your right to withdraw your permission at any time. You will be treated the same no matter what you decide. You will not be giving up any of your legal rights by signing this ICF. For further questions or problems with this study, contact **[*ENTER CONTACT NAME*]**, the **[*CONTACT PERSON'S TITLE*], at [*TELEPHONE NUMBER*].** For questions about your rights as a research participant, contact **[*ENTER NAME OF CONTACT PERSON AT THE IRB/IEC*]** at the **[*IRB/IEC NAME*]** at **[*TELEPHONE NUMBER*]**.

CONSENT STATEMENT

I have read/been read and understand the ICF for the research study called, "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM." I have also discussed with the research staff the purpose of the study, the procedures involved, the possible risks and benefits involved, and the protection of the rights of research participants who join in this study.

I have been given the opportunity to ask questions, which have been answered to my satisfaction. I have been told that any questions that I might have will be answered verbally or if I prefer, with a written statement.

I have reviewed the risks and benefits of being in this research study. I have been told that it is my decision whether or not to participate. I understand that I can change my mind about being in this research study at any time and it will not affect my medical care.

Please carefully read the statements below and think about your choice. No matter what you decide, it will not affect your care. Please select one of the following options:

☐	I agree to have all my blood, urine, saliva (spit), and sputum samples stored and used for future research, inclusive of human genetic research related to TB and possibly other diseases (for example, HIV infection or diabetes) that may have an effect on TB.	Participant's Initials and Date: _____
☐	I agree to have all my blood, urine, and sputum samples stored and used for future research, exclusive of human genetic research related to TB and possibly HIV infection and other diseases.	Participant's Initials and Date: _____

I voluntarily agree to take part in this research study and agree to sign below:

Participant's Name (Print)	**Participant's Signature (or Thumbprint) and Date/Time**
Participant's Authorized Legal Representative's Name (Print) *(As appropriate)*	**Authorized Legal Representative's Signature and Date/Time**
Research Staff's Name Conducting Consent Discussion (Print)	**Research Staff's Signature and Date/Time**
Witness's Name (Print) *(As appropriate)*	**Witness's Signature and Date/Time**
Mother's Name (Print) *(As appropriate)*	**Mother's Signature and Date/Time**
Father's Name (Print) *(As appropriate)*	**Father's Signature and Date/Time**

Copy of Signed and Dated Consent Offered ☐ Yes ☐ No
Participant Accepted Signed and Dated Copy ☐ Yes ☐ No

APPENDIX B: SAMPLE ASSENT FORM ACTIVE PULMONARY TB (COHORT A)

For the protocol: "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM"
(RePORT INTERNATIONAL COMMON PROTOCOL)

You have been invited to join this research study because you may have active tuberculosis (TB) of the lungs. A research study is a way to learn more about people. The purpose of this research study is to learn more about people with TB and other related diseases, by collecting sputum (the mucous that you cough up), urine (pee), saliva (spit), and blood samples. These samples will be stored in a laboratory, which we will call a "biobank." Researchers or doctors who have special permission will use these samples to learn more about TB and related diseases.

If you decide that you want to be part of this study you will be asked to:

- Answer some questions to make sure you are eligible (will be able) to be in the study.
- Be in this study for about 1 year, but it may be longer depending on what kind of TB medicines you are taking.
- Come to the clinic at least 4 times – at Entry, Month 1, Month 2, and at the end of your TB treatment (usually 6 months after you join the study).
- Complete a final visit 6 months after you finish your treatment (usually about 1 year after you join the study). This visit can be done in the clinic or by phone.
- Come in at other times if your TB medicines are not working, or you get sick again after you finish your TB medicines, or if you decide you want to stop being in the study.

There are some things about this study that you should also know:

- We will look at your medical reports to double check that you might have TB and what kind of medications you have taken.
- If you are eligible (able to be in the study) and you want, and agree to take part in the study, we will collect sputum (the mucous you cough up), urine (pee), saliva (spit), and blood from you to send to the "biobank."
- We will do a test on your sputum (the mucous you cough up) to make sure you have TB and to see which medicines might work and might not work.

- If you have a hard time coughing up sputum (mucous you cough up), we may ask you to breathe in a steam-like mist through a mask. This mist will help you cough deeply and make it easier to get a sputum sample. We may also put a tube down your nose to get a sample from your stomach.
- We will also collect some blood and saliva (spit) to look at your genes. Genes are your body's instructions to make and operate your body. Some studies may see how certain genes affect a person's ability to fight TB, or how a person responds to TB treatment. Future genetic (or gene) studies on your samples will be related to TB and possibly other diseases (for example, HIV infection or diabetes) that may affect the course of TB in a person. We are not planning to do any tests that would affect how a doctor treats you or anybody in your family. These results will only be used for research.
- We will also do some blood tests to check to see if you have certain diseases.
- In some situations, we will use the blood that we have collected from you to check for HIV. If you have HIV, we will do another test called a CD4 count to tell us how well your body can fight the HIV and other infections.
- We will also do a chest x-ray to look at your lungs, if you did not have one done by your regular doctor.
- We will ask you questions about how you are feeling at each visit and check to see if you are taking your medicines.

Are there big dangers or risks?

There are no big dangers or risks to you by being in this study, but you should know that:

- You might feel uncomfortable when we collect blood from you. You may have some bleeding or bruising where the needle goes into you.
- We won't take more blood than is allowed.
- If you do have a tube placed in your nose, this might feel uncomfortable.
- There is a small chance that someone may learn that you are in the study and use the information without your or your parents'/legal guardian's permission. We will not write your name on any of your records to make sure that people do not accidentally learn that you are in this TB study.

Are there any benefits?

A benefit means that something good happens to you. You should know that there will not be a benefit to you if you are in this study; but, you will get some laboratory test results that may give you and your doctor information about your health. The main reason you may want to be in this study is to help the researchers and doctors learn how to help people with TB in the future.

When we are finished with this study, we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you don't want to be in the study, your medical care will not change at all. If you decide to be in the study and then later stop, that's okay too. Your parents/legal guardian know about the study too.

If you decide you want to be in this study, please write and sign your name, and write the date and time below.

I, _____, want to be in this research study.

_____ _____

(Sign your name or place thumbprint here) (Date/Time)

APPENDIX C: SAMPLE INFORMED CONSENT FORM HOUSEHOLD CONTACTS (HHC) TO ACTIVE CASE OF TB (COHORT B)

For the protocol: "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM"
(RePORT INTERNATIONAL COMMON PROCOTOL)

BACKGROUND INFORMATION

NOTE: If you are a parent or legal guardian of a child participant "you" refers to "your child" throughout this document.

You have been invited to join this research study because you have lived with or been close to a person who has active tuberculosis (TB) of the lungs, and you may be at risk of developing TB. Researchers are trying to learn more about TB. Much of TB research is done using human samples, such as blood, sputum (the mucous that you cough up), saliva (spit), and urine (pee). We are asking you to let us store some of your samples and your health information in a "biobank" and database so they might be used in future research studies. By using your samples and health information, researchers hope to find new ways to find, treat, and cure TB, and also to prevent TB. Some of these studies may lead to new drugs, vaccines, or tests for TB. These future studies will include genetic and nongenetic studies. Genetic studies focus on your genes. Genes are your body's instructions to make and operate your body. Some studies may see how certain genes affect a person's ability to fight TB, or how a person responds to TB treatment. Future genetic studies on your samples will be related to TB and possibly other diseases (for example, HIV infection or diabetes) that may affect the course of TB in a person. We are not planning to do any tests that would affect how a doctor treats you or anybody in your family. These results will only be used for research.

WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this study is to create a "biobank," which is a collection of body specimens from many people. These specimens are stored in a laboratory. Only researchers and staff working on the study, or who have special permission, will have access to (be able to use) the samples in the biobank. We are creating this biobank so a researcher can use the specimens to study TB or other diseases that may affect TB now or in the future.

A researcher's study must be approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC). These committees help make sure your rights are protected and that you are safe. If the IRB/IEC approves the study, then the researcher may be given permission to use the specimens. The biobank will not give the researcher any information that could identify you, like your name or address. You will not be told the results of the tests conducted on the specimens in the biobank, because they will

be done in the future and are not used for clinical care.

You have the choice to take part in this research study, or not. This Informed Consent Form (ICF) gives information to help you decide. Please read it carefully and take all the time you need to make your choice. Be sure to ask us as many questions as you want. Everyone who takes part in this research study should know that:

- Taking part may involve some risks, but these risks are minimal.
- Taking part is voluntary. If you choose to participate and then later want to stop, you can quit at any time.
- No matter what you decide, now or in the future, it will not affect your medical care.

HOW MANY PEOPLE WILL BE ENROLLED INTO THIS RESEACH STUDY?

We plan to enroll approximately [*EACH RePORT CONSORTIA WILL FILL IN THEIR ENROLLMENT TARGETS FOR COHORT A*] people who have lived with or have been close to someone with active TB of the lungs and about [*EACH RePORT CONSORTIA WILL FILL IN THEIR ENROLLMENT TARGETS FOR COHORT B*] people with active TB of the lungs.

HOW LONG WILL I BE IN THE STUDY?

You will be in this study for about 24 months, or 2 years.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide that you would like to be in this study, we will ask you to sign this ICF. We will offer you a signed copy to keep. Here is what will happen next:

We will ask you some questions to make sure you are eligible to be in this study. If you are eligible and you decide to join this research study, you will be seen in the clinic at least once (at Entry). In addition, you will either come into the clinic or receive a phone call **[RePORT consortia *CRUS MAY ALSO ADD HOME VISITS IF BEING DONE AS PART OF AN AFFILIATED STUDY THAT IS CONDUCTING HOME VISITS.*]** at 4 to 6 months, 12 months, and 24 months after your Entry Visit to see if you have developed any signs or symptoms of TB. **[*IF THERE WILL BE AN AFFILIATED STUDY, THE FOLLOWING TEXT WILL BE INCLUDED, AS APPLICABLE: THESE VISITS [*RePORT consortia *CRU TO ENTER APPLICABLE COMMON PROTOCOL STUDY VISITS] MAY BE ON THE SAME DAY AS THE [CRU TO ENTER AFFILIATED STUDY NAME, AS UNDERSTOOD BY THE PARTICIPANT*] *VISITS*]**. If you do develop signs or symptoms of active TB in the 24 month follow-up period, we ask that you notify our research team, and you will be asked to return once again for a thorough review to see if you have active TB and to collect specimens from you. If you do have active TB, you may be asked to join the study again as a person with TB disease.

After you have read and signed this ICF, the following evaluations will be done in the clinic:

1. Before the Entry Visit

   The following will be done to make sure you are eligible to be in the study:

   a. Medical History and Current Health Status Reviews: We will review information about your medical history; whether or not you have had close contact with someone who has active TB of the lungs; and check whether or not you have signs or symptoms of active TB.

2. Entry Visit:

   If you are eligible, and you want to be in the study, you will be enrolled by having an Entry Visit. We will ask you some questions about yourself. We will also ask you for some contact information so we can remind you and call you for your visits or to check to see how you are doing. In addition, the following evaluations will be done:

   a. Medical History and Current Health Status Reviews: We will again review information about your medical history and check your current health status to make sure you don't have active TB.

   b. We will do a ***[CRU TO ENTER WHICH TEST WILL BE DONE – "Tuberculin Skin Test (TST)" or a "blood test called IGRA"]*** unless a result is already available from your medical record. The test confirms whether or not you have the TB germ in your body, even though you are not sick. ***[*****CRU TO INCLUDE DESCRIPTION FOR TEST BEING DONE AT THE SITE. For TST: "**A small needle is placed under the skin on your forearm containing a substance that tells us if you have the TB germ. You have to come back to the clinic in 2 to 7 days so we can look at your arm and see if the test is negative or positive. **FOR IGRA:** "A small amount of blood is taken (3 mLs) and (***[*****CRU TO ADD PEDIATRIC AMOUNT, IF APPLICABLE*****]*** mLs for children) and sent to the laboratory for testing."*]*

   c. Urine Collection: For storage in the biobank, we will collect about 10 mLs (2 teaspoons) of urine.

   d. Saliva (Spit) Collection: This will be for storage in the biobank to look at your genes. We will collect about 6 mLs (about 1 teaspoon). **[RePORT consortia *CRU TO ADD INFORMATION IF SAMPLES WILL NOT BE COLLECTED FROM CHILDREN LESS THAN 5 YEARS OF AGE*].**

3. Follow-Up Visits: Month 4 to 6, Month 12, Month 24:

   At follow-up visits, we will either have you come into the clinic or we will call you. During these calls or visits, we will ask you about your health status to see if you have developed any signs or symptoms of active TB like a cough, bloody sputum, fever, night sweats, or unexplained weight loss.

4. TB Illness Follow-Up Visit

If you get sick and you think you might have TB or if your doctor tells you that you have active TB, we will ask you to come to the clinic. The following evaluations will be done:

a. Medical History and Current Health Status Reviews: We will ask you questions about your TB signs and symptoms, and we may review your medical information if you had a regular medical visit since your last visit.

b. Sputum Collection: This will be used to check your TB status (a smear and culture), which will tell us if you have active TB. If you do have active TB, we will check to see which medicines might work and might not work. We will also send a specimen for storage in the biobank. If you have a hard time coughing up sputum, you may be asked to breathe in a steam-like mist through a mask. This mist will help you cough deeply. Some children may require a gastric aspirate (stomach sample). This will help the doctor know whether or not TB is making your child sick. This involves putting a small flexible tube in the nose and down to the stomach to get a specimen to test for TB.

c. Blood Collection: This will be for storage in the biobank, including a sample to look at your genes. If we find out that you have active TB, we will also check to see if you have anemia and diabetes. An HIV test will be done if you do not know your HIV status and you are 18 years of age or older, or you are a child born to an HIV-positive mother and have not been tested in the last 90 days. If you are HIV-positive, an additional test called a CD4 count may be done to check your immune status, which can tell us how well your body can fight infections. HIV counseling will also be provided. We will collect 31.5 mLs (about 6 teaspoons) or 15.5 mLs (about 3 teaspoons) **[RePORT consortia *CRU TO MODIFY CHILD VOLUME TO INCLUDE HIV, CD4, CBC, AND HBA1C*]**, if your child is less than 5 years of age.

d. Saliva (Spit) Collection: This will be for storage in the biobank to look at your genes. We will collect about 6 mLs (about 1 teaspoon). **[RePORT consortia *CRU TO ADD TEXT IF SAMPLES WILL NOT BE COLLECTED FROM CHILDREN LESS THAN 5 YEARS OF AGE*.]**

e. Urine Collection: This will be for storage in the biobank. We will collect about 10 mLs (2 teaspoons) of urine.

f. Chest X-Ray: This will be done if one was not done as part of your regular medical care. We will keep a copy of your chest x-ray as part of your study records that may be used in future studies.

5. Premature Discontinuation Visit:

If you must stop the study early or you decide you want to come off the study for any reason, we will either have you come into the clinic or we will call you for a final visit. The following evaluations will be done:

a. Medical History and Current Health Status Reviews: We will again review information about your medical history and check your current health status to make sure you don't have active TB. If we

think you might have TB, we will ask if you would be willing to come in for a TB Illness Follow-Up Visit.

WHAT ARE THE POSSIBLE RISKS?

The samples being taken for biobank storage may be taken during routine medical care and procedures.

There is minimal risk to you if you decide to participate in this study. The following describes some of the possible risks:

- Drawing blood may cause some discomfort, bleeding, and/or bruising where the needle enters the skin. In rare cases, there may be fainting or infection.
- The IRB/IEC only allows a certain amount of blood to be drawn in 1 day for your safety. We will only take an amount that is allowed by the IRB/IEC.
- There are no risks with coughing up sputum or breathing steam-like mist to help with deep coughing.
- A gastric aspiration (getting a stomach sample) is a simple procedure that involves putting a small flexible tube down your child's nose. This may cause minimal discomfort and/or cause your child to gag.
- Chest x-rays are done as part of routine medical care. The amount of radiation emitted during a chest x-ray is small and poses no significant risks to you. If you are pregnant, you will not be required to have a chest x-ray.
- There is a small risk that someone may use your health information and data from the study without proper permission. This incorrect use of information may cause discrimination, distress, or other problems to you. In order to reduce this risk, your name or any personal information will not be written on the research records; research results will not be written in your medical records, and all records will be placed in locked cabinets in locked rooms. Only people working on the study, or who have special permission, will be able be able to see your information, including the information in the database in the computer.

WHERE WILL THE SAMPLES AND INFORMATION BE STORED?

Researchers will store your samples at the local clinical research site and then ship them to the RePORT consortia biobank. There is a possibility that researchers may send the samples to other researchers in your country or outside of your country.

Researchers will store your study information electronically in computer databases.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to us and we will make every effort to protect it. Here are just a few of the steps we will take:

- Only study code numbers will be used on your samples and study information. Your identity will not be known by the researchers who study your samples and health information. Published results will not include your private information.
- We will keep the list that links the code number to your name separate from the samples and information. Only certain study staff can access this list. We will keep the samples in locked freezers in locked buildings. We will keep health information and research information on secure computers. These computers have many levels of protection.
- An IRB/IEC will review and approve the research done on the samples collected for storage at the biobank.

WHO WILL SEE MY PRIVATE INFORMATION?

Apart from the research staff, representatives from the IRBs/IECs, funding organizations of this research study, and regulatory agencies may request to see your private information. In addition, your private information may be provided to national authorities as required by law

HOW LONG WILL RESEARCHERS STORE MY SAMPLES?

Researchers will store your samples for up to 15 years after study completion. However, you can change your mind and withdraw your permission to store them at any time.

WHAT ARE THE POSSIBLE BENEFITS?

This study will not help you directly; but, if you become ill with TB, you will receive clinical laboratory test results that may give you and your doctor information about your health (for example, complete blood count). The main reason you may want to take part is to help researchers make discoveries that might help you and other people now and in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you. You **[RePORT consortia *CRU TO MODIFY: WILL/WILL NOT*]** be paid **[RePORT consortia *CRU TO INCLUDE COMPENSATION THAT WILL BE PROVIDED, IF APPLICABLE*]**. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits. If you experience injury as part of this research study, **[RePORT consortia *CRUS TO ADD WHAT CARE IS TO BE PROVIDED, PER IRB/IEC REQUIREMENTS*]**.

WHAT ARE MY OPTIONS?

Taking part in this study is your choice. You can choose to take part or not to take part. If you choose to

take part, you can change your mind at any time.

WILL I BE TOLD IF THERE ARE NEW FINDINGS?

You will be given clinical laboratory test results that are done for this study if you become ill with TB. These results may give you and your doctor information about your health, specifically about TB, anemia, diabetes, and HIV.

You will not get test results from the samples that are collected for the biobank. These samples will be used by researchers in the future; and therefore, we will not have any test results to share with you. If you are interested in learning whether or not there are new findings in the future, you may contact **[*ENTER NAME OF CONTACT PERSON*] at [*TELEPHONE NUMBER*]**.

WHAT IF I CHANGE MY MIND?

You can decide to withdraw your permission whenever you want. If you decide to withdraw your permission, contact the research staff. There are two ways to withdraw your permission. You could allow researchers to remove all your personal identifiers linked to your stored samples, so that they are not linked to you anymore. These samples will then become anonymous. Or, you can ask researchers to destroy the samples. However, in either case, researchers will not be able to destroy samples or information from research that is already underway. If some tests have already been completed on your samples, any remaining samples will be destroyed. If you withdraw your permission, there will be no negative effects for you.

WHY WOULD THE RESARCH DOCTOR TAKE ME OFF THIS RESEARCH STUDY?

The research doctor may need to take you off the study early without your permission if the study is cancelled by the funding organizations or by the IRB/IEC. The research doctor may also take you off early if you get active TB or you are not able to attend the visits as required by the research study. Another reason the doctor may take you off this research study is if you develop other health problems that will make you unable to participate.

WHAT ARE MY RIGHTS AND WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

It is your right to decide if researchers can collect, store, and use your samples and information for research purposes. It is also your right to withdraw your permission at any time. You will be treated the same no matter what you decide. You will not be giving up any of your legal rights by signing this ICF. For further questions or problems with this study, contact **[*ENTER CONTACT NAME*]**, the **[*CONTACT PERSON'S TITLE*]** at **[*TELEPHONE NUMBER*].** For questions about your rights as a research participant, contact **[*ENTER NAME OF CONTACT PERSON AT THE IRB/IEC*]** at the **[*IRB/IEC NAME*]** at **[*TELEPHONE NUMBER*]**.

CONSENT STATEMENT

I have read/been read and understand the ICF for the research study called, "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM." I have also discussed with the research staff the purpose of the study, the procedures involved, the possible risks and benefits involved, and the protection of the rights of research participants, who join in this study.

I have been given the opportunity to ask questions, which have been answered to my satisfaction. I have been told that any questions that I might have will be answered verbally or if I prefer, with a written statement.

I have reviewed the risks and benefits of being in this research study. I have been told that it is my decision whether or not to participate. I understand that I can change my mind about being in this research study at any time and it will not affect my medical care.

Please carefully read the statements below and think about your choice. No matter what you decide, it will not affect your care. Please select one of the following options:

☐	I agree to have all my blood, urine, saliva (spit), and sputum samples stored and used for future research, inclusive of human genetic research related to TB and possibly other diseases (for example, HIV infection or diabetes) that may have an effect on TB.	Participant's Initials and Date: _____
☐	I agree to have all my blood, urine, and sputum samples stored and used for future research, exclusive of human genetic research related to TB and possibly HIV infection and other diseases.	Participant's Initials and Date: _____

I voluntarily agree to take part in this research study and agree to sign below:

Participant's Name (Print)	**Participant's Signature (or Thumbprint) and Date/Time**
Participant's Authorized Legal Representative's Name (Print) *(As appropriate)*	**Authorized Legal Representative's Signature and Date/Time**
Research Staff's Name Conducting Consent Discussion (Print)	**Research Staff's Signature and Date/Time**
Witness's Name (Print) *(As appropriate)*	**Witness's Signature and Date/Time**
Mother's Name (Print) *(As appropriate)*	**Mother's Signature and Date/Time**
Father's Name (Print) *(As appropriate)*	**Father's Signature and Date/Time**

Copy of Signed and Dated Consent Offered ☐ Yes ☐ No
Participant Accepted Signed and Dated Copy ☐ Yes ☐ No

APPENDIX D: SAMPLE ASSENT FORM HOUSEHOLD CONTACT TO ACTIVE CASE OF TB (COHORT B)

For the protocol: "COMMON PROTOCOL FOR COLLECTING DATA AND SPECIMENS FROM PARTICIPANTS IN THE REGIONAL PROSPECTIVE OBSERVATIONAL RESEARCH FOR TUBERCULOSIS (RePORT) CONSORTIUM"
(RePORT INTERNATIONAL COMMON PROTOCOL)

You have been invited to join this research study because you have lived with or been close to a person who has active tuberculosis (TB) of the lungs, and you have a chance of getting TB. A research study is a way to learn more about people. The purpose of this research study is to learn more about people with TB and other related diseases, by collecting sputum (the mucous that you cough up), urine (pee), saliva (spit), and blood samples. These samples will be stored in a laboratory, which we will call a "biobank." Researchers or doctors who have special permission will use these samples to learn more about TB and related diseases.

If you decide that you want to be part of this study you will be asked to:

- Answer some questions to make sure you are eligible (will be able) to be in the study.
- Be in this study for about 2 years.
- Come to the clinic at least one time at the Entry Visit.
- Either come to the clinic or talk to someone by phone at the follow-up visits. **[RePORT consortia *CRUS MAY ADD HOME VISITS IF THE COMMON PROTOCOL IS AFFILIATED WITH ANOTHER PROTOCOL THAT IS CONDUCTING HOME VISITS.*]** These visits or phone calls will take place at 4 to 6 months, 1 year, and 2 years after you join the study. At these visits, we would like to see if you may have gotten active TB.
- Come in for another visit if we think you may have gotten active TB.

There are some things about this study that you should also know:

- We will look at your medical records and ask you questions to make sure you have been in close contact or living with someone with active TB and whether or not you have signs or symptoms of TB.
- If you are eligible (able to be in the study) and you want, and agree to take part in the study, we will do a ***[*CRU TO ENTER WHICH TEST WILL BE DONE – "Tuberculin Skin Test (TST)" or a "blood test called IGRA"*]*** unless a result is already available from your medical record. The test tells us whether or not you have the TB germ in your body, even though you are not sick. ***[*CRU TO**

INCLUDE DESCRIPTION FOR TEST BEING DONE AT THE SITE. For TST: "A small needle is placed under the skin on your forearm containing a substance that tells us if you have the TB germ. You have to come back to the clinic in 2 to 7 days so we can look at your arm and see if the test is negative or positive. **FOR IGRA:** "A small amount of blood is taken (3 mLs) and (*[***CRU TO ADD PEDIATRIC AMOUNT, IF APPLICABLE***]* mLs for children) and sent to the laboratory for testing."*]*

- We will collect urine (pee), saliva (spit), and blood from you to send to the "biobank" at the Entry Visit.
- At follow-up visits in the clinic or by phone **[RePORT consortia** ***CRUS MAY ADD HOME VISITS IF THE COMMON PROTOCOL IS AFFILIATED WITH ANOTHER PROTOCOL THAT IS CONDUCTING HOME VISITS.*****]**, we will ask you about your health, how you are feeling, and whether or not you have any signs or symptoms of TB like a cough, blood in your sputum (mucous), fever, night sweats, or weight loss.
- If you do get sick and we think you have TB, we will ask you to come to the clinic to do the following:
  - We will ask you questions about how you are doing and look at your medical information if you went to see a doctor.
  - We will do a test on your sputum (the mucous you cough up) to see if you have TB. If you do have active TB, we will check to see which medicines might work and might not work.
  - If you have a hard time coughing up sputum (mucous), we may ask you to breathe in a steam-like mist through a mask. This mist will help you cough deeply and make it easier to get a sputum sample. We may also put a tube down your nose to get a sample from your stomach.
  - We will collect sputum (the mucous you cough up), urine (pee), saliva (spit), and blood from you to send to the "biobank."
  - We will also collect some blood and saliva (spit) to look at your genes. Genes are your body's instructions to make and operate your body. Some studies may see how certain genes affect a person's ability to fight TB, or how a person responds to TB treatment. Future genetic (or gene) studies on your samples will be related to TB and possibly other diseases (for example, HIV infection or diabetes) that may affect the course of TB in a person. We are not planning to do any tests that would affect how a doctor treats you or anybody in your family. These results will only be used for research.
  - If we find out that you have TB, we will also do some blood tests to check to see if you have certain diseases.

- In some situations, we will use the blood that we have collected from you to check for HIV. If you have HIV, we will do another test called a CD4 count to tell us how well your body can fight the HIV and other infections.
- We will also do a chest x-ray to look at your lungs, if you did not have one done by your regular doctor.

Are there big dangers or risks?

There are no big dangers or risks to you by being in this study, but you should know that:

- You might feel uncomfortable when we collect blood from you. You may have some bleeding or bruising where the needle goes into you.
- We won't take more blood than is allowed.
- If you do have a tube placed in your nose, this might feel uncomfortable.
- There is a small chance that someone may learn that you are in the study and use the information without your or your parents'/legal guardian's permission. We will not write your name on any of your records to make sure that people do not accidentally learn that you are in this TB study.

Are there any benefits?

A benefit means that something good happens to you. You should know that there will not be a benefit to you if you are in this study; but, you will get some laboratory test results that may give you and your doctor information about your health. The main reason you may want to be in this study is to help the researchers and doctors learn how to help people with TB in the future.

When we are finished with this study, we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you don't want to be in the study, your medical care will not change at all. If you decide to be in the study and then later stop, that's okay too. Your parents/legal guardian know about the study too.

If you decide you want to be in this study, please write and sign your name, and write the date and time below.

I, _____, want to be in this research study.

_____ _____

(Sign your name or place your thumbprint here) (Date/Time)