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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U.S. National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS)
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LIST OF ABBREVIATIONS AND ACRONYMS

AFB	Acid-Fast Bacilli
BJGMC	Byramjee-Jeejeebhoy Government Medical College
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
DBT	(India) Department of Biotechnology
DECIT	Brazilian Ministry of Health, Department of Science and Technology
DNA	Deoxyribonucleic Acid
DOST	(Philippines) Department of Science and Technology
DR	Drug-Resistant
DS	Drug-Susceptible
DST	Drug Susceptibility Testing
EOT	End of TB treatment
FIOCRUZ	Fundação Oswaldo Cruz
GCLP	Good Clinical Laboratory Practice

GCP	Good Clinical Practice
HbA1c	Hemoglobin A1C (Glycated Hemoglobin)
HHC	Household Contact
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
INA RESPOND	Indonesia Research Partnership on Infectious Diseases
INH	Isoniazid
IRB	Institutional Review Board
JIPMER	Jawaharlal Institute of Postgraduate Medical Education and Research
LTBI	Latent Tuberculosis Infection
MDR/XDR	Multidrug-Resistant/Extensively Drug-Resistant
MMRC	Modified Medical Research Council (Dyspnea scale)
MOP	Manual of Operating Procedures
MRC	(South Africa) Medical Research Council
mRNA	Messenger Ribonucleic Acid
Mtb	Mycobacterium Tuberculosis
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
PBMC	Peripheral Blood Mononuclear Cell

PCHRD	Philippine Council for Health Research and Development
PI	Principal Investigator
PID	Participant Identification Number
PPD	Purified Protein Derivative
PTLD	Post-Tuberculosis Lung Disease
RePORT	Regional Prospective Observational Research for Tuberculosis
RNA	Ribonucleic Acid
SATVI	South Africa Tuberculosis Vaccine Initiative
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
UCT	University of Cape Town
WHO	World Health Organization

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PROTOCOL SCHEMA

PURPOSE: The primary purpose of the RePORT International project, which RePORT ***[ENTER HOST COUNTRY]*** is a part of, is to provide a platform for coordinated 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 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 for individuals presenting with symptoms of active TB and their close or household contacts (HHCs). All participants will be screened for TB at baseline. Participants will provide clinical data and specimens for specifically-defined Common Protocol research purposes, at baseline and at specific time points. Participants with active pulmonary TB (Cohort A) will be followed during the national standard of care the treatment period **[*ENTER HOST COUNTRY TREATMENT PERIOD E.G., 4 OR 6 MONTHS]*** and after the treatment period for a total study period of at least 12 months. Participants who are close contacts or HHCs of a person with active case of TB (Cohort B) will be followed for 12 months. Cohort A participants without active TB will not be followed after baseline. Cohort B participants with TB at baseline will not be followed after baseline, but may be eligible for transfer to Cohort A. Biospecimens will be banked by RePORT ***[ENTER HOST COUNTRY]*** in aliquots described by the RePORT International Laboratory Manual in preparation for future analysis.

POPULATION: Cohort A patients presenting with active pulmonary TB symptoms must be 15 years of age or older. There are no age restrictions for Cohort B participants. Participants in either cohort may be co-enrolled in an affiliated study (also known as Parent Protocol), 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 secure funding to support these cohorts from the NIH/NIAID/DAIDS and host countries 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 the study for the duration of TB treatment

and after the treatment period for a total period of at least 12 months. Cohort B participants will be on the study for 12 months.

PRIMARY OBJECTIVE: To provide specimens and linked clinical data to perform collaborative and epidemiological research, leading to a better understanding of the prognosis of TB disease and the pathogenesis of progression from TB exposure and infection to active disease. The intent is that data and specimens will be used by the RePORT ***[ENTER HOST COUNTRY]*** Consortium to perform epidemiological and biomarker research in collaboration with RePORT and other national and international collaborators, through agreements and understandings to be determined by the RePORT ***[ENTER HOST COUNTRY],*** RePORT International Executive Committee (EC) ***[AND/OR ENTER OTHER GOVERNING BODY(IES), AS APPLICABLE].***

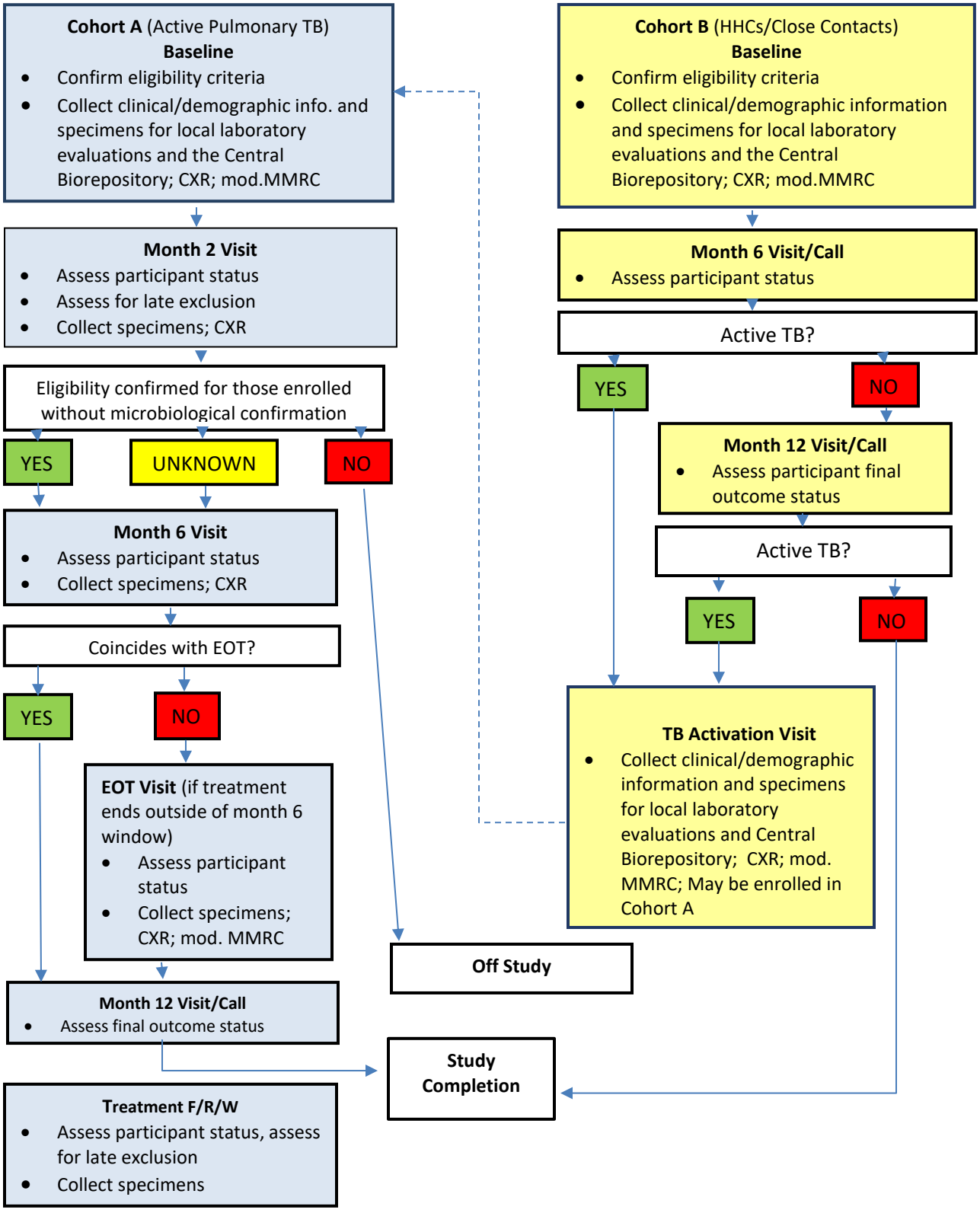
STUDY SITES: RePORT consortia have been established in Brazil, China, India, Indonesia, Philippines, and South Africa, and are being established in South Korea and Uganda. Data and bio-specimen repositories are being developed in each country to store their own data and samples. Each RePORT consortium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

STATISTICAL AND DATA MANAGEMENT CENTER: Each Network consortium will maintain its own Statistical and Data Management Center for initial data collection and interaction with TB RICC Statistical Center.

CENTRAL BIOREPOSITORY: Each Network consortium will have its own central biorepository, coordinating with RePORT International Biorepository guidelines.

RePORT International Coordinating Center (RICC): 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. TB RICC 3.0 is comprised of investigators from Rutgers University/New Jersey Medical School, Vanderbilt University Medical Center, Frontier Science Foundation, Johns Hopkins University, and FioCRUZ. TB RICC 3.0 is charged with the management, development and implementation of RePORT International Consortium-wide activities, policies and protocol development and adherence.

PROTOCOL SCHEMA DIAGRAM



1. Background

Tuberculosis (TB) and HIV/AIDS are the two major 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 host biomarkers that correlate with the likelihood that a new drug or drug regimen will be effective. These investigations require biological specimens collected from well-characterized active pulmonary TB participants and contacts or household contacts (HHCs) of infectious TB cases who are at risk of progressing to active TB. These specimens could then be made available for a variety of purposes, including development of diagnostic 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 host biomarkers to serve as a surrogate endpoint predicting efficacy of prevention and treatment modalities or to improve diagnostics for adults and children. 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) is supporting, along with Host Country or Regional Teams, development of individual cohort studies of active pulmonary and latent TB and a forum for collaborative research. The RePORT International Consortium presents a 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 several teams of India- and US-based investigators, to implement individual cohort studies of active and latent TB in India (2013). In 2013, the Brazilian Ministry of Health, Department of Science and Technology (DECIT) and US NIH began 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. And in 2016, the US NIH, in collaboration with the South Africa Medical Research Council (MRC), established a RePORT consortium comprising investigators from across the country in studies of adults and children, with and without HIV/AIDS. RePORT Philippines is a multi-organizational, collaborative effort that was initiated by the Philippine Council for Health Research and Development (PCHRD) of the Department of Science and Technology (DOST) in August 2017 through a Memorandum of Understanding with the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health (NIH). Established in 2017, the RePORT China consortium is a collaborative network with the leadership and funding from China TB Clinical Trial Consortium (CTCTC), Innovation Alliance on TB Diagnosis and Treatment (Beijing) (IATB), and with technical support from NIH. RePORT Korea started as part of a collaboration between the National Institute of Infectious Disease (NIID) of the Korea National Institute of Health (KNIH) recently in 2023. The Division of Bacterial Disease Research of the Center for Infectious Disease Research under the NIID oversees RePORT Korea. The ultimate aim of RePORT Korea is to build a foundation for multinational collaboration to facilitate communication among tuberculosis researchers. In conjunction with other TB research activities supported by NIH in Uganda, RePORT Uganda is a multi-national effort under the leadership of Makerere University, and the Ugandan Ministry of Health – starting in 2023.

1.2 Study Objectives

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

- Screening, triage, and diagnosis of TB disease
- The outcomes of treated TB disease
- The pathogenesis of progression from TB exposure to disease.

The intent is that data and specimens may be used by the RePORT ***[ENTER HOST COUNTRY]***

Consortium while also being harmonized for sharing both nationally and internationally, through agreements and understandings to be determined by sites, country consortia and a governing board of the consortia.

1.3 Description of the Population

The Common Protocol will enroll individuals seeking care who have symptoms of untreated active pulmonary TB (Cohort A) and those who were recently exposed to someone with active TB (Cohort B). Additional protocols/modules are in development to study multi drug resistant (MDR) TB and extensively drug-resistant (XDR) TB, extrapulmonary TB, post-TB lung disease (PTLD), pediatric TB, and TB diagnostics, including adults and children with possible, but not-yet diagnosed TB, as well as populations for future TB vaccine work. The invention of this Common Protocol is to provide a mechanism and template 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 ***[ENTER HOST COUNTRY]*** 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

2.1 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 ENTER AFFILIATED STUDY, IF APPLICABLE]***, for the biorepository, and any inconvenience for clinic ***[and ENTER ADDITIONAL STUDY VISITS, IF APPLICABLE (IF THERE IS AN AFFILIATED STUDY)]***. 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 (for

example, TB infection status) and samples will be linked by this PID rather than by participant name or any other identifier.

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.

2.2 Potential Known Benefits

The long-term goal of this study is to provide quality-controlled 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 prospective observational cohorts: the first with participants presenting with symptoms of active pulmonary TB (Cohort A) and the second with participants who are a close contact or HHC of 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 controlled biostorage for future studies. Samples will be curated, stored, and managed at the RePORT ***[ENTER HOST COUNTRY'S]*** Central Biorepository. The resultant "bank" of biological samples will be made available to investigators participating in or collaborating with the RePORT ***[ENTER HOST COUNTRY]*** Consortium through a peer-review process that considers high-priority, credible proposals for their use, plus all the necessary institutional and governmental approvals. ***[IF THE COMMON PROTOCOL IS CONDUCTED IN CONJUNCTION WITH AN AFFILIATED STUDY, THEN INCLUDE THE FOLLOWING TEXT: 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.]*** Each RePORT Network has the option of collecting and storing additional samples (e.g., urine, saliva, sputum, whole blood for PBMCs and PAXgene tubes, oral swabs) not specified in this protocol.

Example uses for stored specimens include but are not limited to:

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. **Sputum** for messenger ribonucleic acid (mRNA), microbiologic measures, and host immune markers.

While this valuable resource will be primarily for use within ***[ENTER HOST COUNTRY]***, it is expected that the "bank" will also be available to investigators external to the RePORT ***[ENTER HOST COUNTRY]*** Consortium, 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 samples and testing in participants beyond what is normally collected or tested for patients 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. Future tests will also be conducted under an IRB/IEC approved protocol. 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 samples for specifically-defined 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 either sign a separate Common Protocol Informed Consent Form (ICF), or a Parent Protocol ICF that includes these study activities. 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 post treatment for at least 12 months after enrollment (e.g., approximately 6 months post-treatment if the treatment regimen is 6 months or 8 months post-treatment if the treatment regimen is 4 months).

Participants will be requested to provide samples at Baseline, Month 2, Month 6, End of Treatment (usually combined with Month 6 visit), 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 12 Month Visit/Call 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). Participants may be contacted in between visits to remind them of upcoming study visits and standard of care visits.

If blood collection volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by ***[ENTER COUNTRY SPECIFIC GUIDELINES, AS APPLICABLE]*** or local IRB/IEC guidelines, specimens will be prioritized as outlined in the RePORT International Laboratory Manual. Samples will also be collected if the participant voluntarily withdraws from the study prior to the 12 Month 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 ENTER AFFILIATED STUDY, IF APPLICABLE]*** at the CRU, 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. Cohort A participants 18 years of age or older and children born to an HIV-positive mother must provide documentation of HIV status or be willing to be tested for HIV, though they can participate regardless of the test 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 ENTER AFFILIATED STUDY, IF APPLICABLE]*** within the preceding 6 months. Drug susceptibility testing (DST) will be performed as part of the study procedures.

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 suspected, but not yet confirmed active pulmonary TB (newly diagnosed or TB relapse), excluding known multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB), will be recruited into the study. If active pulmonary TB is not confirmed (see Section 4.2.3, Late Exclusion Criteria), individuals will subsequently be excluded from the active pulmonary TB cohort. Their specimens (or a subset), however, may be retained as control samples.

4.2.1 Inclusion Criteria

A CRU may impose stricter screening criteria to be consistent with local or national guidelines, but to be considered eligible for enrollment in the Common Protocol, an individual suspected of having newly diagnosed TB or TB relapse, excluding known MDR and XDR TB**,** (see Section 4.4, Outcome Measures for Cohort A for the definition of TB relapse) must meet the following criteria:

1. Presents with the following:

    a. Presumed drug-susceptible (D) TB case: Signs or symptoms consistent with active pulmonary TB that include, but are not limited to: persistent cough, hemoptysis, fever, fatigue or lethargy, night sweats, or pleuritic chest pain (see the MOP for definitions).

2. Has documentation of one of the following:

    a. CXR findings consistent with TB;
    b. Sputum smear or culture-positive by microscopy**; or** Mtb detection by rapid diagnostic test, such as Gene Xpert or Line Probe Assay (LPA).

3. Has documentation of, or willingness to be tested for HIV infection. Participants born to an HIV-positive mother must provide documentation of HIV status (confirmed positive test any time in the past or last negative test within 90 days prior to the Screening Visit) or be willing to be tested as part of the study.

4. Has provided written consent or witnessed oral consent in the case of illiteracy, prior to his/her first sample or other study-specific data being collected, or in the case of minors, parents/legal guardians have provided consent and minors have provided assent, as dictated by the CRU's IRB/IEC and country-specific regulations.

5. Agrees to the collection and storage of blood and sputum specimens for use for future research. RePORT Networks/CRUs may require the collection of additional specimens such as urine, saliva, and oral swab.

6. 15 years of age or older.

4.2.2 Exclusion Criteria

Individuals already diagnosed with pulmonary TB, but not responding to treatment with first-line standard anti-TB drugs, e.g., persistent symptoms or persistently positive microbiology results, and are thus suspected to have MDR or XDR TB are NOT eligible for enrollment into Cohort A. They may be enrolled into a separate cohort of MDR/XDR TB individuals under a separate protocol.

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 12 Visit).

2. Has an active psychiatric condition, or alcohol or drug dependence that, in the opinion of the site investigator or designee, might interfere with the ability to give true informed consent and to adhere to the study requirements.

3. Is currently imprisoned.

4. Received >1 week (daily or intermittent doses) of any drugs with anti-TB activity within 30 days prior to provisional enrollment, including:

    i. First line anti-TB drugs in any combination: isoniazid (INH), rifampicin, pyrazinamide, ethambutol, and streptomycin;

    ii. Fluoroquinolones: e.g., ofloxacin, ciprofloxin, levofloxacin, moxifloxacin, nalidixic acid, sparfloxacin, and gatifloxacin;

    iii. Injectable second line anti-TB drugs: e.g., kanamycin, amikacin, and capreomycin;

    iv. Oral second line anti-TB drugs: e.g., p-aminosalicylic acid, cycloserine, terizidone, ethionamide, prothionamide, thiocetazone; or

    v. Other bacteriostatic second-line anti-TB drugs: e.g., clofazamine, linezolid amoxicillin/clavulanate, imipenem/cilastin, meropenam, clarithromycin, bedaquiline, and delamanid.

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

4.2.3 Late Exclusion Criteria

Cohort A participants will be withdrawn from the study if they do not meet the following criteria within the first two months:

Culture-confirmed pulmonary TB (regardless of age or initial smear results) from at least one of the following: Mtb identified by liquid or solid culture of expectorated or induced sputum from a clinical or study-related sample.

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

Participants who fail to meet the TB confirmation criteria above will be withdrawn from the study. However, specimens that were previously collected from the participant as part of the study 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

Eligibility will be verified before evaluations at the Baseline Visit are performed. The following evaluations will be performed or abstracted from the participant's medical chart at the Baseline Visit:

1. Demographics, medical history, targeted concomitant medication history, and clinical data and completion of respiratory questionnaire [modified MMRC Dyspnea Scale].

2. CXR, if not done as part of standard of care **[or as part of ENTER AFFILIATED STUDY, IF APPLICABLE]** within 4 weeks prior to the Baseline Visit (not required for pregnant participants).

3. Local laboratory evaluations

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

   a. HIV test per the **[ENTER HOST COUNTRY'S]** national guidelines (if required; see Section 4.2.1, 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. DST for first-line anti-TB drugs for all participants.

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

   f. Gene Xpert

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 (plasma)

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

Each RePORT Network has the option of collecting and storing additional samples (e.g., urine, saliva, sputum, whole blood for PBMCs and PAXgene tubes, oral swabs).

4.3.3 Month 2/8 Week Visit (−2 weeks/+2 weeks)

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 Month 2 evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. Eligibility confirmation when possible (see Section 4.2.3, Late Exclusion Criteria)
    b. TB treatment history (including clinical and laboratory evaluations)
    c. TB treatment adherence
    d. TB signs and symptoms
    e. Targeted concomitant medications
2. CXR, if not done as part of standard of care
3. Local laboratory evaluations
    a. Sputum smear and culture (when specimen can be obtained)

4. Specimen collection for Central Biorepository storage

   Whole blood (plasma) will be collected for Central Biorepository storage (see the Report International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures.) Each RePORT Network has the option of collecting and storing additional samples (e.g., urine, saliva, sputum, whole blood for PBMCs and PAXgene tubes, oral swabs).

4.3.4 Month 6/26 Week Visit (−4 weeks/+6 weeks)

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

The following Month 6 Visit evaluations will be performed:

1. Medical history (participant status) since the previous visit:
   a. TB treatment history (including clinical and laboratory evaluations)
   b. TB treatment adherence
   c. TB signs and symptoms
   d. Targeted concomitant medications
2. CXR, if not done as part of standard of care
3. Local laboratory evaluations
   a. Sputum smear and culture (when specimen can be obtained)
4. Specimen collection for Central Biorepository storage

   Whole blood (plasma) will be collected for Central Biorepository storage (see the Report International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures.). Each RePORT Network has the option of collecting and storing additional samples (e.g., urine, saliva, sputum, whole blood for PBMCs and PAXgene tubes, oral swabs).

4.3.5 End of Treatment Visit

The End of Treatment (EOT) Visit will take place when the participant completes his/her prescribed TB treatment regimen**.** Participants will not complete an EOT Visit if the end of their TB treatment regimen falls within the Month 6 Visit window and they completed the Month 6 Visit.

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 during the EOT Visit:

1. Medical history (participant status) since the previous visit:
    a. TB treatment history (including clinical and laboratory evaluations)
    b. TB treatment adherence
    c. TB signs and symptoms
    d. Targeted concomitant medications
    e. Modified MMRC Dyspnea Scale
2. CXR, if not done as part of standard of care
3. Local laboratory evaluations
    a. Sputum smear and culture (when specimen can be obtained)
4. Specimen collection for Central Biorepository storage

    Whole blood (plasma) will be collected for Central Biorepository storage (see the Report International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures.) Each RePORT Network has the option of collecting and storing additional samples (e.g., urine, saliva, sputum, whole blood for PBMCs and PAXgene tubes, oral swabs).

4.3.6 Month 12/52 Week Visit/Phone call (-4 Weeks/+6 Weeks)

The final study visit will be conducted 12 months after the baseline visit in person or by phone. This visit may be conducted up to 4 weeks before or 6 weeks after the target visit date. The

following evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. TB treatment history (including clinical and laboratory evaluations)
    b. TB treatment adherence
    c. TB signs and symptoms
    d. Targeted concomitant medications

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 emerging resistance, 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), the participant will be requested to come in for an in-person TX F/R/W Visit as soon as possible. If criteria for emerging resistance, treatment failure, or TB relapse are met, or the participant withdraws from the study for any reason, this will be the participant's final study visit.

The following evaluations will be performed:

1. Medical history (participant status) since the previous visit:
    a. TB treatment history (including clinical and laboratory evaluations)
    b. TB treatment adherence
    c. TB signs and symptoms
    d. Targeted concomitant medications
    e. Modified MMRC Dyspnea Scale

2. Clinical evaluation
    a. Assess for treatment failure or TB relapse, to determine if bacteriologic or clinical outcome criteria have been met (see section 4.4, Outcome Measures for Cohort A)

3. Local laboratory evaluations

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

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

      i. 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 (see the RePORT International Laboratory Manual for specimen collection, prioritization, processing, storage, and shipping procedures):

   a. Mtb isolate subculture

   b. Whole blood (plasma)

5. If the participant has met criteria for bacteriologic or clinical treatment failure or TB relapse, the following will be completed:

   a. 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)

   b. CD4 count if HIV-infected (not required if collected as part of standard of care **[or as part of ENTER AFFILIATED STUDY, IF APPLICABLE]** within the preceding 6 months; data will be abstracted 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 that the participant return to the clinic to complete the HIV test and CD4 count

as soon as possible.

If it has been determined that treatment failure or TB relapse has occurred, 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. All participants, with the exception of those without culture-confirmed TB as described section 4.2.3, will be assigned a treatment outcome, completion of therapy status outcome, and a study outcome. Some participants may also be assigned a clinical outcome and/or meet the definition of an additional classification (See section 4.4-4).

1. **Treatment Outcomes** for participants who initially have bacteriologically-confirmed, DS TB using World Health Organization [15] definitions modified where noted.

    a. **Cured:** a pulmonary TB patient with culture-confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of failure. (*Modified WHO definitions: Bacteriological response refers to bacteriological conversion with no reversion: "bacteriological conversion" describes a situation in a patient with culture-confirmed TB where at least two consecutive cultures, taken at any time during treatment, are negative.)*

    b. **Treatment completed:** A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.

    c. **Treatment failed:** A TB patient with at least 1 positive sputum culture at the end of therapy (e.g. month 4 or month 5 of treatment) or whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy. (*Reasons for the change include: no clinical response and/or no bacteriological response; adverse drug reactions; or evidence of additional drug resistance to medicines in the regimen. The inclusion of a positive sputum culture is a modification to the WHO definition.)*

    d. **Died:** A patient who died before starting treatment or during the course of treatment. (*Patient died for any reason.)*

    e. **Lost to follow-up**: A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months (60 days) or more.

f. **Not evaluated:** A TB patient for whom no treatment outcome was assigned. (*This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown; however, it excludes those lost to follow-up.)*

g. **Treatment success:** The sum of cured and treatment completed. (If possible, patients should be assigned an outcome of Cured or Treatment completed which will be combined to determine who meets this definition)

h. **The WHO treatment outcome "Sustained treatment success" will not be assigned.**

2. **Clinical Outcomes**

Some participants with baseline 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/cure:** A patient presenting resolution of the signs/symptoms consistent with TB by the end of therapy (not bacteriologically-confirmed). (*The patients without symptoms consistent with TB at the beginning of the therapy cannot have their clinical response evaluated.)*

b. **Clinical failure:** The persistence, relapse, or progression of signs/symptoms of tuberculosis (e.g. fever, sweats, productive cough, weight loss, worsening on chest X-ray, evidence of progressive extra-pulmonary tuberculosis) in a participant who has completed four months of anti-TB treatment.

c. **Clinical relapse:** Clinical or radiological evidence of active tuberculosis after completion of therapy (i.e. during the follow-up period). Participant met the definition for Clinical response/cure above, or Treatment outcome of bacteriologic *Cure* or bacteriologic status indeterminate with *Treatment complete*.

3. Completion of Therapy Status

In addition to assigning a treatment outcome (section 4.4-1), all participants will be assigned a "Completion of Therapy Status", with the exception of those without culture-confirmed TB as described in Section 4.2.3.

a. **Completion of adequate therapy:** Considered accomplished when the participant who does not meet criteria of *Treatment failure*, meets criteria for *Treatment complete*, and has received at least 90% of the recommended number of doses, per national guidelines, of multidrug anti-TB therapy within 1 year of treatment initiation.

b. **Incomplete:** Treatment is considered not complete when the participant discontinues the treatment during two or more months before the stipulated time (e.g., 6 months on regimens with rifampin, or when there were delays in the treatment) or does not complete at least 90% of the recommended number of doses, per national guidelines, of multidrug anti-TB therapy within 1 year of treatment initiation. Discontinuation of therapy may be due to any cause: treatment failure, intolerance or toxicity, drug-resistance detection, withdrawal from the study by the patient or the investigator, lost to follow-up and death. In all these cases, the Principal Investigator and/or the attending physician should determine the need for additional therapy, and the follow-up shall be maintained as originally planned.

4. Additional Classifications

These classifications may ALSO be assigned under specific circumstances.

a. **Bacteriologic relapse*:** Participant met criteria for *Cured* or *Treatment complete* 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 includes either a true relapse or a new episode of TB caused by reinfection [16].

b. **Emerging resistance:** A participant who has Mtb with 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).

5. Study Outcomes

All participants will be assigned a *Study Outcome*.

a. **Completed all study activities:** A participant who completed TB treatment and completed all study visits/calls.

b. **Death:** A participant who dies for any reason after consenting to participate and prior to the end of study. (A participant may have already been assigned a bacteriological or clinical outcome post treatment. If the participant died during treatment, he/she will also have "died" as the Treatment outcome.)

c. **Lost to follow up:** A participant who did not come to the study visits or did not answer any telephone call or could not be contacted for 60 days or more; or a participant who did not start treatment or whose treatment was interrupted for 60 days or more.

d. **Mandatory withdrawal:** A participant without culture-confirmed TB as described in Section 4.2.3.

e. **Other:** participant does not meet any of the above criteria.

4.5 Schedule of Events for Cohort A - Active Pulmonary TB

Activities	Screening	Baseline	Month 2	Month 6 (-4 wks to +6 wks)	EOT[d]	Month 12 (-4 wks to +6 wks)	TX F/R/W
Informed Consent	X						
Eligibility Assessment	X	X					
Eligibility confirmation (assess for late exclusion)			X				X
Demographics, medical history, clinical data		X					
Participant status			X	X	X	X	X
CXR[a]		X	X	X	X		
Respiratory questionnaire (MMRC Dyspnea Score)		X			X		X
HIV test[b]		X					X
CD4 count if HIV-infected		X					X
CBC and lymphocyte count		X					
HbA1c		X					X
Sputum smear & culture[c]		X	X	X	X		X
Sputum DST		X					X
Gene Xpert		X					
Mtb isolate subculture for storage		X					X
Plasma for storage		X	X	X	X		X

[a] Pregnant participants are not required to have CXR.
[b] HIV testing on participants not known to be positive to be performed per national guidelines
[c] Sputum will be collected at follow-up visit if it is producible.
[d] EOT Visit only if treatment end does NOT fall within 6 month Visit window.

5. Cohort B: Household Contacts (HHCs) or Close Contacts of Active TB Patients

5.1 Design and Procedures

Participants who are at high risk for progression to active TB will have the option of participating in the Common Protocol. Recent HHCs or close contacts of an infectious case of TB will be recruited into Cohort B. The main goal of Cohort B will be to identify individuals who progress from TB exposure to active TB over an approximate 12-month time span. Some individuals, such as individuals with HIV infection, may be offered and prescribed isoniazid prophylaxis once identified as a contact of a patient with 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 in the study will be required to sign a Common Protocol ICF or provide consent as part of the Country's Parent 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 up to 12 months (12 month visit with a 6 week window). Participants will be requested to give samples at the Baseline Visit. Additional samples will be collected if a participant develops active TB within the follow-up period, 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 [**Enter country 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 all 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. There must have been at least 4 hours/week of contact within the past 6 months after the onset of symptoms of the index-case. Preference will be given to household contacts, but all close contacts are eligible.

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 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. Willing to undergo HIV and IGRA testing.

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 12 Visit).

2. Has an active psychiatric condition, or alcohol or drug dependence that, in the opinion of the site investigator or designee, might interfere with the ability to give true informed consent and to adhere to the study requirements.

3. Is currently imprisoned.

4. Presumed TB.

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 – HHCs/Close Contacts to Active Cases of 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.

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, targeted concomitant medication 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.

   Note: Some RePORT International consortia have decided to repeat TST or IGRA on subsequent study visits if a HHC is negative on first exam, though it is not currently a required element of the Common Protocol, Cohort B. If this is the case, include a statement such as: Protocol Participants who are TST or IGRA negative will be asked to return to the clinic to reassess their TST or IGRA status within 4 to 12 months after the Baseline Visit.

3. Completion of respiratory questionnaire [Modified MMRC Dyspnea Scale].

4. Specimen collection for testing

   a. Sputum (if producible) for Gene Xpert and culture

   b. Blood draw for HbA1c testing

5. 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 RNA)

   b. Whole blood (plasma)

c. Whole blood (genetic analyses)

d. Sputum (if producible)

6. Chest x-ray

5.3.3 Follow-Up Visits Month 6 (26 Weeks) and Month 12 (52 Weeks), - 4 Wks to +6 Wks

Follow-up visits may be conducted by phone or in-person [**if Host Country RePORT has decided to have initial TST/IGRA-negative participants return for re-testing, add a statement like the following: However, individuals who were TST or IGRA negative at baseline will be asked to return for a clinic visit to re-assess their TST or IGRA status.]** The following evaluations will be conducted:

1. Medical history (participant status)

   a. TB prophylaxis (e.g., INH, INH/rifampin, or other regimen) and TB treatment history

   b. TB signs and symptoms

   c. Abstraction of laboratory and/or CXR information from medical records.

   d. Targeted concomitant medications

   e. Determination of final outcome status at Month 12 visit

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, INH/rifampin, or other regimen) and TB treatment history

   b. History of TB signs and symptoms

   c. Abstraction of laboratory and/or CXR information**.**

2. 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 as part of the ENTER AFFILIATED STUDY, IF APPLICABLE]** (not required for pregnant participants)

3. Targeted concomitant medications

4. Completion of respiratory questionnaire [Modified MMRC Dyspnea Scale]

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 as part of ENTER AFFILIATED STUDY, 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 <15 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 ENTER AFFILIATED STUDY, 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 as part of ENTER AFFILIATED STUDY, 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 as part of ENTER AFFILIATED STUDY, IF**

APPLICABLE]; abstract the data from the participant's medical chart or research record).

If results are pending and a determination of definite, probable, or possible TB cannot be made, specimens for laboratory tests b-e 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.

6. 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 RNA)

   c. Whole blood (plasma)

   d. Whole blood (genetic analyses)

   e. Sputum

5.3.5 Premature Discontinuation Visit or Phone Call

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 or phone call 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 ENTER AFFILIATED STUDY, IF APPLICABLE]

   d. Targeted concomitant medications

   e. Determination of final outcome status

5.4 Outcome Measures for Cohort B

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 12-month follow-up period.
2. **Definite TB:** Culture-confirmed or GeneXpert-confirmed Mtb from any anatomical site over the 12-month follow-up period.
3. **Probable TB:**
    a. Signs or symptoms consistent with active TB that include persistent cough, hemoptysis, fever, 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 of MTBC.
4. **Possible TB:**
    a. Signs or symptoms consistent with active TB that include persistent cough, hemoptysis, fever, 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).
5. **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.

c. **Withdrawal:** For any reason.

5.5 Schedule of Events for Cohort B - Household Contacts to Active Cases of TB

Activities / Visit	Screening	Baseline	Month 6 (- 4 wks to + 6 wks)	Premature Discontinuation Visit[c]	Month 12 (-4 wks to +6 wks)	TB Activation
Informed Consent	X					
Eligibility Assessment	X	X				
Demographics, medical history, clinical data		X				
Participant status		X	X	X	X	X
Respiratory questionnaire (MMRC Dyspnea Score)		X				X
CXR[a]		X				X
IGRA or TST		X				
Smear and culture from TB activation site						X
Mtb isolate subculture for storage						X
Gene Xpert		X				
Sputum culture		X				
Sputum DST						X
Sputum for storage (if producible)		X				X
Whole blood (PAXgene) for storage		X				X
Whole blood (genetic analyses) for storage		X				X
Plasma for storage		X				X
HIV test if status is unknown[b]						X
CD4 count if HIV-infected						X
CBC and lymphocyte count						X
HbA1c		X				X

[a] Pregnant participants are not required to have CXR.
[b] HIV testing on participants not known to be positive to be performed per national guidelines
[c] Participants who meet criteria for premature discontinuation other than TB activation should have a final study visit or phone call at the time it is decided to terminate study participation.

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. The following required baseline biorepository specimens are not collected:

        i. Sputum for culture and Mtb isolate

        ii. Plasma for storage

    b. More than 1 week of anti-TB therapy (listed under the exclusion criteria) is received before the collection of sputum for culture and Mtb isolate (see Section 4.2.3, Late Exclusion Criteria) and pulmonary TB diagnosis is not confirmed as defined by the protocol (see Section 4.2.3, Late Exclusion Criteria)

    c. An HIV test was not completed within 7 weeks of enrollment

    d. Emerging resistance; the participant may re-enroll into an MDR or XDR cohort, if all eligibility criteria are met for the separate protocol.

    e. Completion of 12 month visit

    f. Treatment failure (bacteriologic or clinical) [OPTIONAL- CRU may continue to follow participant]

    g. TB relapse (bacteriologic or clinical) [OPTIONAL- CRU may continue to follow participant]

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 12 Visit; the participant may enroll into Cohort A if all eligibility criteria are met.

    b. Completion of the Month 12 Visit.

    c. The linked Cohort A participant does not have TB.

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 must stop for other administrative reasons.

7. Sample Size

[THIS SECTION WILL BE MODIFIED BASED ON HOST COUNTRY SAMPLE SIZE PLANS]

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, digital imaging, 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.

8. Participating Cohort Research Units

Currently, RePORT consortia have been established in Brazil, China, India, Indonesia, Philippines, South Africa and are being established in South Korea and Uganda. Other country networks are expected to be added, helping to spur TB treatment and prevention research around the world. Each consortium reflects national research goals but is coordinated through utilization of common standards and practices that are delineated by the RePORT International Common Protocol with corresponding case report forms and manuals 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.

9. Individual Country Cohorts

9.1 RePORT India

Both Indo-US governments have further supported the scientific research goals of RePORT India by expanding the number of sites represented across the country, especially by involving scientists and participants from the Northern and North-eastern parts of the country. In addition to the existing group of TB patients and their household contacts across nine Indian sites in the RePORT India Phase II Common Protocol, the consortium plans to support the enrollment of 1500 adult and child patients who are suspected of having TB inside or outside their lungs, 588 adult patients with TB inside the lungs, and 794 household contacts of adult patients with TB inside the lungs.

Under a Phase II Common Protocol, RePORT India is pursuing five specific scientific aims including the following cohorts: Diagnostic (New TB suspects), Cohort A (Active TB disease), and Cohort B (HHCs). Samples collected under this protocol will be curated, stored, and managed at the RePORT India Central Biorepository at NIRT where Phase I Common Protocol samples are currently stored. A data management center has been established at JIPMER in Puducherry and PPD will continue to provide technical support. The Phase II Common Protocol Co-Chairs are: Drs. Kamakshi Prudhula Devalraju (BMMRC) and Robert Bollinger (JHU). The consortium has been expanded to include two new CRSs in Northern India. RePORT India Phase II now is extended to September 2026. While Phase II is set to be extended until September 2026, RePORT India is gearing up discussions setting up the grounds for Phase III. In Phase III, there will be a greater emphasis on making use of samples collected in Phases I & II to answer the regional TB questions that are still unanswered.

Efforts will be made to nurture collaborations with Indian entities and additional Indian Research/academic Institutions in collaborative efforts with US counterparts to perform regional research with global standards.

Phase III will also emphasize the generation of more scientific publications and utilizing RePORT India's resources in grant applications. In Phase III, RePORT India will enhance its collaboration with TB RICC and RePORT India's Common Protocol will be synchronized with TB RICC protocols to allow efficient integration of data collected in Phase III with RePORT International studies to answer global TB questions.

9.2 RePORT Brazil

Investigators are funded directly by NIH and co-funded by the Government of Brazil and will be enrolling into a single protocol which is harmonized with the RePORT International Common Protocol. Two sites in Rio de Janeiro, one in Manaus, and one in Salvador were selected to enroll up to 2,000 active TB cases and 4,000 close contacts of those TB cases. Vanderbilt University Medical Center 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 prophylaxis 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 is located in Salvador at the Instituto Brasileiro de Reabilitação (IBR), part of the Fundação José Silveira.

9.3 RePORT South Africa

RePORT South Africa is a network of 6 SA and 4 US institutions established to evaluate biomarker approaches to detect symptomatic and subclinical TB disease. The project core team is based at the University of Cape Town. The leadership group (PIs Hatherill and Sterling) works with investigators at 8 clinical sites to implement prospective cohorts based on the RePORT Common Protocol and associated data standards. The consortium builds upon successful partnerships between RePORT investigators at US institutions (Vanderbilt, Colorado State, UCLA, University of Washington) and advanced SA biomarker laboratories (SATVI, UCTLI, SUN-IRG, AHRI). Standardized sample sets are stored at the Biorepository at Stellenbosch University. Data harmonization with RePORT International and the RePORT Brazil network is led by VUMC. The RePORT SA project tests biomarker approaches to detect symptomatic TB, among individuals with symptoms consistent with active disease, and subclinical and incident TB, among household contacts and others at risk for progression to active disease. Performance of novel proteomic, metabolomic, transcriptomic, and Mtb DNA biomarkers are being tested at 7 research laboratories, using standardized whole blood, serum, urine, sputum and oral swab sample sets, in study populations that include adults, children, and people living with HIV. The most promising biosignatures, benchmarked against established WHO Target Product Profiles for triage, screening and predictive TB tests, will be evaluated head-to-head and validated in future cross-network RePORT collaborations.

9.4 RePORT Indonesia

The Indonesia network is funded by the NIH and co-sponsored by the Government of Indonesia. The coordination of the consortium within Indonesia is led by the INA-RESPOND Secretariat. This

network participated in the RePORT International Common Protocol for Phase I, specifically adopting Cohort A of the TRIPOD study (Tuberculosis Research of INA-RESPOND On Drug Resistance). This study took place in seven referral hospitals across seven major cities in Indonesia from 2017 to 2021. Out of the 447 subjects enrolled, 260 were identified as newly diagnosed TB cases, while 187 had previously been treated for TB. Both drug-susceptible and multi-drug-resistant patients were monitored from the start to the end of treatment. Drug-sensitive patients were followed throughout their treatment, while MDR patients were tracked for two years. Data and biorepository specimens from the TRIPOD study were harmonized using standardized methods at agreed-upon intervals. Currently, RePORT Indonesia is involved in the second RePORT International project, titled "Analysis of host biomarkers associated with adverse TB treatment outcomes across RePORT International Sites." The TRIPOD study contributed data on 11 failure cases and 22 cure cases for this analysis.

9.5 RePORT Philippines

RePORT Philippines has two sites – the University of the Philippines Manila – National Institutes of Health (UPM-NIH) and the De La Salle Medical and Health Sciences Institute (DLSMHSI). UPM-NIH started study enrolment in June 2018, while DLSMHSI started enrolment in April 2019 with funding from the Philippine Council for Health Research and Development – Department of Science and Technology. For Cohort A - Site 1 led by UPM-NIH collects specimens from patients with drug-sensitive TB while Site 2 led by DLSMHSI collects specimens from patients with drug-resistant TB. For Cohort B, household contacts of index cases in Cohort A are recruited and tested for presence of latent TB infection. Both sites have their respective biorepository of specimens and for both cohorts, the RePORT International Common Protocol was followed. Active recruitment and funding for Phase I of RePORT Philippines UPM-NIH and DLSMHSI ended in February 2023 and April 2023, respectively. With this, the study teams are preparing for Phase II research activities. Phase II will involve the use of the biobanked specimens from Phase I to conduct studies, such as (i) transcriptomic profiling and analyses of LTBI and drug sensitive and drug resistant TB (ii) biomarker discovery and validation studies among adult and pediatric TB cases including those with adverse outcomes, and (iii) pathogenomic and molecular epidemiologic studies. Long term follow up of participants in both cohorts continue as RePORT Philippines embarks on collaborative and cross-consortia projects utilizing the clinico-epidemiologic data and specimens in the biorepository.

9.6 RePORT China

The RePORT China consortium is a collaborative network with the leadership and funding from China TB Clinical Trial Consortium (CTCTC), Innovation Alliance on TB Diagnosis and Treatment

(Beijing) (IATB), and with technical support from NIH. The RePORT China consortium joined RePORT International in January 2017 after signing the RePORT International Memorandum of Understanding. RePORT China followed the bylaws, which set clear guidelines and expectations for current and future groups to work together on a broad set of common goals. China consortium developed a locally-tailored study protocol, manual of laboratory operations, and case report forms (CRFs) for qualified case enrollment, sample collection and storage, data collection and sharing based on the Common Protocol and biorepository standards by RePORT International. Currently, the target enrollment for RePORT China is 180 participants, with the actual number at 198. Samples originated from blood, urine and sputum were collected and stored with the total number at 12,480. Currently 7 sites remain active under RePORT China, including Beijing Chest Hospital, Changsha Central Hospital, The Third People's Hospital of Zhenjiang, Fuzhou Pulmonary Hospital, Tianjin Haihe Hospital, Suzhou Fifth People Hospital, and Jingzhou Chest Hospital.

9.7 RePORT South Korea

RePORT South Korea started as part of a collaboration between the National Institute of Infectious Disease (NIID) of the Korea National Institute of Health (KNIH) and the National Institute of Allergy and Infectious Disease of the United States. The Division of Bacterial Disease Research of the Center for Infectious Disease Research under the NIID oversees RePORT South Korea. The ultimate aim of RePORT South Korea is to build a foundation for multinational collaboration to facilitate communication among tuberculosis researchers. To achieve this, RePORT South Korea is providing opportunities for researchers and institutes within the field to participate in international collaborative programs. RePORT South Korea is running two projects to contribute to the consortium. For an international collaborative research (Project I), RePORT South Korea concluded the agreement with De La Salle Medical and Health Science Institute (DLSMHSI) to conduct a cohort study. The study will identify biomarkers for distinguishing patients with latent tuberculosis infection (LTBI) and active disease and predicting the development of tuberculosis in household contacts of patients with active tuberculosis. The NIID is financially supporting this three-year project, and the Division of Bacterial Disease Research is in charge of this collaborative research.

9.8 RePORT Uganda

The implementation of RePORT in Uganda is a positive step towards advancing TB research and improving healthcare in the country. The RePORT consortium is welcome to Uganda, and the teams look forward to implementing the Common Protocol towards advancing TB research and innovation. A number of sites will be involved in RePORT Uganda. **Iganga-Mayuge Health and Demographic Surveillance Site (IMHDSS)** serves as a population-based research platform where demographic and health data are collected from a defined population over time. IMHDSS will

contribute valuable data for TB research and surveillance efforts. The site covers a contiguous and clearly demarcated area of 155km^2, a part of Iganga and a part of Mayuge districts. It is made up of 65 villages in seven sub-counties and it is enclosed by 16 health centres and a hospital. Currently, the HDSS covers a population of 90,000 people from 17,000 households, about 59% living in rural areas. **Jinja Regional Referral Hospital is** a regional referral hospital for Eastern Uganda, it offers outpatient, inpatients and specialized healthcare services including TB case management. RePORT activities at this site will involve clinical research, patient care, and capacity building. The site is actively enrolling study participants in a number of diagnostic studies including Novel and Optimized Diagnostics for Pediatric TB in Endemic Countries and Accuracy of Novel Diagnostic Tests for Detection of Tuberculosis in Adults (FEND-TB).

Integrated Biorepository of H3Africa Uganda (IBRH3AU) is an integrated biorepository at Makerere University College of Health Sciences under the NIH's H3Africa initiative. IBRH3AU provides a resource of well-characterized and annotated high quality biospecimens for future use by researchers as well as trainers. This resource serves both communicable and non-communicable disease researchers in Africa. The ultimate goal of IBRH3AU is to improve the prevention, diagnosis, and treatment of illness and the promotion of health throughout society. All activities are done in adherence to current SOPs and GCLP standards. The quality assurance program covers the pre-analytical, analytical, and post-analytical phases. This is through standard procedures like sample rejection/acceptance, routinely monitored Turn-Around-Time, Internal Quality Controls (IQCs), External Quality Assessment (EQA) proficiency programs, Blind/Split sample testing, etc. IBRH3AU is currently in its advanced stage preparations for SANAS/SADCAS accreditation. The biorepository is also equipped with state-of-the-art Genomics, Molecular and Immunology laboratories that process biospecimens and add value. IBRH3AU will be key in the long-term storage and shipment of biospecimens collected under the REPORT protocol. IBRH3AU currently supports research studies in East and Central Africa.

The Genomics, Molecular, and Immunology Laboratories (GMI Labs) are diagnostic, research, and training facilities, focused on both infectious and non-infectious diseases or conditions. The GMI Laboratories provide laboratory services to all healthcare providers, including physicians, researchers, epidemiologists, students, and all healthcare policymakers, for the benefit of patients and the global community. GMI offers quality diagnostic, training, and research services using the most advanced Genomics, Molecular, and Immunology techniques while complying with the ISO 15189:2012 requirements for medical laboratories.

CAP-accredited Mycobacteriology Laboratory (BSL-3) is a College of American Pathologists (CAP) – accredited Biosafety Level (BSL)-3 culture facility. It is a site for multinational tuberculosis research initiatives namely: the Division of AIDS Clinical Trials regional TB diagnostic laboratory

(DAIDS/ACTG/RTBDL) and the International Maternal, Paediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network, and the Global Alliance for TB drug development studies. This facility has vast experience in clinical trials including those for novel tuberculosis drugs for treating MDR-TB for example, the laboratory participated in the BPaMZ regimen for MDR-TB treatment. Other clinical trials include those for both susceptible and resistant TB with study numbers in public databases [NCT02410772 (TBTC study 31, S31/A5349), NCT02193776 (NC-005-(J-M-Pa-Z), NCT01380080 (REMEMBER, ACTG 5274), IMPAACT P1078 (DAIDS ID 10732), ISRCTN63579542, NCT02342886 (NC-006-(M-Pa-Z)) among others. It has participated in several diagnostic evaluation studies some of which have made it to WHO policies most recently being the multi-country Xpert ULTRA evaluation study. The CAP accredited BSL-3 offers clinical and research TB diagnostic services according to WHO and international guidelines.

Uganda Supra National Reference Laboratory (SRL) was started as the Uganda Bacteriological Investigation Unit in the late 1950's under the then East African Community. The laboratory participated in anti TB clinical trials and drug toxicities under the then British Medical Research Council (MRC). After the collapse of the East African Community in 1970's, the laboratory reverted to the line ministries. Its name changed to Central Tuberculosis laboratory (CTBL) in 1980's and National Tuberculosis Reference Laboratory in the 1990'S. The Uganda National Tuberculosis Reference Laboratory established under the National Tuberculosis and Leprosy Programme (NLTP) of the Ministry of Health (MoH) received accreditation from the WHO in April 2013, making it the first SRL in East Africa, and the second in Sub-Saharan Africa to achieve this status. SRL supports the integration of quality TB diagnostic services for the purpose of providing prompt and accurate results to patients according to the International Standard of Care with national laboratory strategic plans, incorporating cross cutting laboratory issues including supply management, specimen transport, and referral and human resource development. SRL aadvocates for TB laboratory worker protection with use of current WHO TB bio-safety recommendations. It supports the development of monitoring and evaluation indicators starting with a good data management system. SRL is part of the National TB and Leprosy Program Uganda (NTLP).

IDI-African Center of Excellence in Bioinformatics & Data-intensive Sciences (ACE) in partnership with the US Government National Institute of Allergy and Infectious Diseases (NIAID) and the Office of Cyber Infrastructure and Computational Biology (NIH/NIAID/OCICB) established the African Centre of Excellence in Bioinformatics & Data Sciences, one of the 2 such centres on the African continent. ACE is focused on bioinformatics and data-intensive research in the context of infectious diseases, including TB. It provides expertise in data analysis, informatics, and bioinformatics to support TB research and improve data management.

These sites collectively, create a strong foundation for the RePORT Uganda Chapter, enabling a comprehensive approach to TB research, diagnostics, patient care, and capacity building. The collaboration among these institutions will contribute to significant advancements in TB control and treatment in Uganda.

10. RePORT International Coordinating Center (RICC)

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. TB RICC 3.0 is comprised of investigators from Rutgers University/New Jersey Medical School, Vanderbilt University Medical Center, Frontier Science Foundation, Johns Hopkins University, and FIOCRUZ. TB RICC 3.0 is charged with the management, development and implementation of RePORT International Consortium-wide activities, policies and protocol development and adherence.

TB RICC 3.0 is developing the mechanisms by which consortia can share data and specimens. The RICC is establishing a RePORT International leadership and governance structure that includes regular reviews of data quality and completeness, updating and distributing SOPs and MOPS, and ensuring cross-consortia harmonization through discussion and bylaws adherence. The TB 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 scientific and leadership meetings as needed.

11. Data Collection

Each clinical site and specimen repository is expected to have a trained Data Manager to provide oversight over all procedures as specified within the MOP (Manual of Operating Procedures). RePORT International has developed a set of case report forms (CRFs) that all RePORT International consortia are expected to utilize with as little modification as possible. The RePORT ***[ENTER HOST COUNTRY]*** consortium will be expected to collect and store the information required to implement the Common Protocol according to detailed specifications designed to facilitate future data sharing. These Common Protocol elements may be embedded into a Network's "Parent Protocol" or be solely a cohort designed to follow the Common Protocol. A Data Elements Bank has been assembled in spreadsheet format, which will accompany each CRF. The Data Elements Bank details each question asked within the CRFs for the Common Protocol and are listed in the order they appear on the CRF. In addition to listing the data attributes of long and short name, type, format, and permissible outcomes for each question, the Data Bank also includes a tag that specifies which questions can and cannot be modified from their current state. Data

delivered by the RePORT ***[ENTER HOST COUNTRY]*** consortium will be evaluated against the Data Elements Bank to ensure adherence to the requirements of MOP data collection procedures. The same scenario applies to the Specimen Collection Schedule of Events of the Common Protocol - the Networks may collect only these biologic specimens, or in addition to other specimens as per their Network protocol.

11.1 Clinical Data Collection

TB RICC will establish a centrally-defined REDCap project of the CRFs required by the Common Protocol following all formatting, skip logic, and range checks specified in the Data Elements Bank. The centrally developed REDCap project will be fully verified and validated as defined by current industry standards following a robust software development lifecycle. Sites are strongly encouraged to implement the RePORT International CRFs using the centrally developed REDCap system to ensure for the capture of high quality data that is aligned to the Data Elements Bank. Adhering to this requirement will further reduce the number of necessary data queries, will better facilitate data requests, and will streamline data harmonization efforts. Sites can implement the centrally-defined REDCap project and store all data locally at an institution within the specified host country. Each country and host site will remain fully in the control of their own REDCap project and can choose what level of access to provide TB RICC.

11.2 Network Unique Identifiers

All participant-related study information will be identified through the PID (Patient Identifier) that will be collected on all CRFs. **PIDs must be unique to each individual participant and must be assigned consistently on all data, specimens, and other study artifacts collected from each individual.** 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 be made available to authorized representatives from regulatory and funding organizations as required. For Repository storage of cohort samples, RICC is available to review and suggest a common framework, or when sharing samples across Networks, RICC will work to ensure valid sample identification.

11.3 Quality Assurance

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 collectively serve as source documents for the study are located in the MOP.

11.4 Statistical and Data Management Center

Statistical and Data Management Centers (SDMCs) will be located in the individual RePORT consortia. The ***[ENTER STATISTICAL AND DATA MANAGEMENT CENTER NAME]*** will be the statistical and data management center (SDMC) for the RePORT ***[ENTER HOST COUNTRY]*** CRUs. The SDMC will provide centralized data management training (such as for REDCap) to the CRUs and additional training and refresher training as needed. See the MOP for detailed information on data management and ***[ENTER SDMC NAME]*** roles and responsibilities. TB RICC will establish a RePORT International leadership and governance structure that will be responsible for conducting regular reviews of data quality and completeness, updating, and distributing SOPs and MOPS to all participating entities, and ensuring for overall cross-consortia harmonization. A minimum set of data elements will be shared by the SDMC of each host country with TB RICC on a routine basis. This dataset will fulfill the RePORT International defined goals of establishing centralized interactive dashboards, allowing investigators to better evaluate concept sheet feasibility, and reporting to sponsors on key items such as enrollment and demographic summaries. Establishing such routine data transfer between the host country SDMC and TB RICC will be expected to reduce the need for host country data management teams to produce and submit multiple/overlapping data sets. Routine data transfer as described above is however not expected to meet the needs of all data requests and as such supplemental transfers in support of specific concept proposals may still be necessary. All use of harmonized data will be subject to review and approval by the RePORT Executive Committee and any sharing or release of data will be governed by the concept sheet approval process.

12. Specimens for Long-Term Storage at the Network's 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 12.1). Samples will then be shipped to the Network's 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 Network's 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.

12.1 Central Biorepository Study Specimen Collection and Storage Chart *(Some of the specimens listed below are optional)*

Specimen Type		Volume
Whole blood[a] (PAXgene RNA)		2.5 mL
Whole blood[a] (IGRA)		3 mL (1 mL/tube)
Whole blood (genetic analyses)		4 mL (BD EDTA)
PBMC		10 mL (BD Heparin)
Plasma		Harvested from BD Heparin (PBMC) tubes above
Sputum		Whatever volume is possible to collect
Extracted host RNA		Prepared from PAXgene tube
Mtb isolate	**Cohort A**	Subculture of original Mtb isolate, and relapse or failure isolate
	Cohort B	Subculture of confirmatory Mtb isolate from each participant who develops active TB

[a] 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.

13. Ethical Conduct of the Study

All participating CRUs must be in compliance with U.S., Host 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 E6(R2) (GCP). Should regulations and guidelines differ between countries, the more restrictive regulations and guidelines will apply.

The Country Network's 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.

13.1 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 minors as required by ***[ENTER HOST COUNTRY]***-specific regulations and IRB/IEC policies. If the minor 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 minor refuses, then he/she will not be enrolled, even if the parent consents.

13.2 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 personally 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.

13.3 Study Discontinuation

The study may be discontinued at any time by the IRB/IEC, a government agency such as the ***[ENTER FUNDING ORGANIZATION(S)]*** or NIH, or other national agencies that have regulatory oversight.

14. 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 RePORT ***[ENTER HOST COUNTRY]*** Publication Guidelines maintained ***[ENTER LOCATION OF GUIDELINES]***.

15. 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.

16. Quality Assurance and Cohort Research Unit Support Visits

The study will be conducted in compliance with the protocol, MOP, RePORT ***[ENTER HOST COUNTRY]*** Consortium Standard Operating Procedures (SOPs), GCP/Good Clinical Laboratory Practice (GCLP), and applicable regulatory requirements in ***[ENTER HOST COUNTRY]*.** Before implementation, the protocol, and all relevant study documents, including recruiting materials,

will be approved by the local IRBs/IECs. The accurate recording of data, record keeping, and archiving of essential documents will be ensured.

A site visit may be conducted in order to ensure compliance with applicable regulations and ethical standards. Sites will be provided with support and assistance 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. See the MOP for information on site visits.

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