Regional Prospective Observational Research for Tuberculosis (RePORT) International

Common Protocol Manual of Operating Procedures

Common Protocol for Collecting Data and Specimens from Participants in the Regional Prospective Observational Research for Tuberculosis (RePORT) Consortium

(RePORT International Common Protocol Version 2.1^{+})

Version* 1.0 | March 26, 2026

*Version 1.0 of the MOP aligns with version 2.1 of the Common Protocol. Either of these documents may be updated to a new version independently. Revision History for the MOP is located at the end of the document.

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RePORT International Manual of Operating Procedures

Version 1.0, 03-26-2026

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1. INTRODUCTION

1. INTRODUCTION

The purpose of this Manual of Operating Procedures (MOP) is to assist country network/country site Principal Investigators (PIs), Study Coordinators, and other study staff with an overview of the site initiation process and implementation procedures for the ***Common Protocol for Collecting Data and Specimens from Participants in the Regional Prospective Observational Research for Tuberculosis (RePORT) Consortium***. (All study procedures should be conducted in accordance with the Common Protocol and this MOP. Background and Mission of the RePORT International Consortium

The RePORT International consortium is sponsored by the National Institutes of Health, Division of AIDS (NIH, DAIDS). The primary purpose of the RePORT International project is to provide a platform for coordinated tuberculosis (TB) research by establishing a common set of standards and definitions. This will enable research studies to produce harmonized data and/or biorepositories that can be easily integrated for combined or cross-analyses. The RePORT International Common Protocol (Version 2.1, 8 July 2024) describes the populations and processes for collecting the specimens and data.

The purpose of the RePORT International Consortium is to:

- Bring together RePORT country networks;
- Advance regional and global TB science;
- Strengthen TB research capacity and infrastructure; and
- Serve as a collaborative entity to foster research collaboration within each RePORT country and internationally, with the aim of carrying out a wide range of basic and clinical research that can lead to the discovery of clinically important biomarkers and aid in the development of vaccines, drugs, and diagnostics.

The Common Protocol may also be supported by a host country, which may implement additional policies, procedures, and standards beyond those prescribed by RePORT. These additional standards are at the discretion of the host country but must minimally meet the standards expected by RePORT, which are expected to produce well-characterized specimens with the purpose of developing reliable TB biomarkers that predict TB treatment response, progression from latent to active disease, and which are needed to advance TB prevention efforts, both in vaccine development and preventive therapy.

Many organizations are involved in RePORT and lend meaningful contributions to the consortium, including:

- Funding organizations
- RePORT International Executive Committee (EC)
- Country networks/country sites
- Host country data management center
- Network biorepositories
- Other entities, as applicable

1.1. RePORT International Consortium Operational Components

This chapter describes the roles and responsibilities of the organizations that work together to support and implement the RePORT International Common Protocol.

1.1.1. RePORT International Executive Committee (EC)

The Executive Committee provides leadership and governance for the Consortium. Specific responsibilities and the members of the EC are outlined in the RePORT International Bylaws located on the RePORT International website home page

1.1.2. Data Management Center (DMC): Roles and Responsibilities

Frontier Science & Technology Research Foundation (“Frontier Science”) will serve as the central Data Management Center (DMC) for the RePORT International Consortium.

The DMC will coordinate the receipt, quality assurance, and compilation of the Common Protocol data from each RePORT country data coordinating center. The DMC will merge the Common Protocol data for EC-approved concept sheets and manage data for RePORT International-approved central activities (e.g., data visualizations and dashboards). The DMC will facilitate data transfers from the participating country sites using the standardized data transfer template, perform data completeness and integrity checks upon data receipt, and be responsible for producing aggregated reports. The details of the DMC roles and responsibilities are described in the sections below.

A. RICC Operations Center Responsibilities

As the DMC, Frontier Science will be responsible for coordinating data management, communications, and operations with each of the country networks/country sites, which principally refers to RePORT country data coordinating centers but may also encompass individual study sites. Each country network/country site will be responsible for the collection and cleaning of data at its site(s). Each country network/country site will develop its own database for data collection. Frontier Science will be responsible for developing and maintaining a data transfer template and accompanying instructions that outline self-management of their site databases and the procedures for transferring data for EC-approved studies and initiatives.

Meetings and Communications

Frontier Science will lead regular and ad hoc meetings/conference calls, as needed, to discuss protocol-related data management activities with the country networks/country sites either through direct calls to the country network/country site Data Manager, site visits, or through the Data Harmonization Working Group of the RePORT International Coordinating Center (RICC). It is recommended that all meetings, emails, and calls with the country networks/country sites be documented to ensure that data management processes are communicated, understood, and followed by each of the country networks/country sites.

Points of Contact

Each country network/country site will appoint a Data Manager who will be responsible for collecting study data to be stored in the central data repository maintained by each RePORT country network. The Data Manager at each country network/country site will be responsible for ensuring data completeness and quality per the Common Protocol. If the country network/country site has developed its own database for entering Common Protocol data, the country network/country site Data Manager will follow the data transfer template maintained by Frontier Science to transfer both data and data corrections (see Section 1.1.4.3 below). The country network/country site Data Manager or their designee will serve as the primary point of contact for all data transfers and queries from Frontier Science, as well as for any necessary site training on local databases (e.g., REDCap, FreezerPro®), data analysis software, and quality assurance practices.

The country network/country site Data Manager or designee and Frontier Science will communicate about the following activities:

- Data collection
- Data cleaning (includes reconciling the clinical and laboratory databases)
- Data harmonization (includes pooling of RePORT country data and mapping of RePORT country data to specified data models for RePORT or other collaborating consortia)
- Data transfers
- Specimen information

- Training needs
- Other activities, as applicable

B. Data Management Responsibilities

This section outlines some of Frontier Science's data management responsibilities.

Clinical Database Development

Frontier Science has developed a data harmonization pipeline that can be used to compile data collected for the Common Protocol, as well as provide quality control (QC) checks to programmatically monitor data quality. The data harmonization pipeline has the ability to perform batch imports of large amounts of data from the country networks/country sites, transform those datasets into the RePORT International data model, and extract the data per data extract parameters defined/approved by the RePORT EC. The database will employ security controls for access, administrative controls for user rights, and an audit trail.

For country networks/country sites that develop their own databases to capture data collected for the Common Protocol, the data completeness and data cleaning should occur prior to transfer to Frontier Science.

'The primary responsibility for maintaining and cleaning the collective Common Protocol data across the consortium for analysis and reporting of RePORT International EC-approved studies and initiatives will reside with Frontier Science. Each country network / country site will maintain their Common Protocol data locally until requested for such studies and initiatives.' Note: prior to having a central data center in place, Cohort A data that has been collected from the early phase of RICC is stored and maintained at Rutgers University.

Each country network/country site will be responsible for procuring, installing, and configuring a Biorepository management system to track specimens collected and stored for the Common Protocol, consistent with systems recommended by the RICC. **FreezerPro® Sample Management System** (*Azenta*, Frederick, Maryland), a web-based sample management solution for inventory, management, and quality assurance of biologic samples (e.g., PAXgene RNA, PBMC, plasma, sputum, urine), has been approved by the EC for use in the Common Protocol. This system can be accessed and configured by each country network/country site as needed. FreezerPro® will be configured to collect pertinent data on specimens, including participant identification number (PID), study visit, specimen type, and freezer location. The system will be used to manage and track specimens from the country network/country site's laboratory to other sites/laboratories for specialized analysis. The responsibility for cleaning the specimen data will reside with the country sites.

Central Data Processing

As the DMC, when Frontier Science receives data transfers from the country networks/country sites, it loads the transferred data into the data harmonization pipeline for preparing analysis datasets. Frontier Science will monitor the quality of data arriving from country networks/country sites using both programmed edit checks and manual review of the data. Frontier Science will issue queries to each country site identified during the central data processing.

Statistical Support

Provisions for statistical support for RePORT International projects will be determined by the funding organization(s) and the RePORT EC. Country networks will supply their own statistical support for projects not part of RePORT International via their protocol teams.

Coordinating Center Statistical Support

Where possible, Frontier Science will develop reports for monitoring data quality for specific EC-approved studies and initiatives. Reports may be requested by the EC to monitor country network/country site performance, including but not limited to accrual and data quality, as well as other reports that may assist with providing a better understanding of specific study progress and guide the future analyses of study results. The frequency of each report will be defined in a data quality plan to be developed and maintained by Frontier Science.

1.1.3. Country Biorepository Database

1.1.3.1. Country Biorepository Roles and Responsibilities

Each host RePORT country will support and manage a local biorepository database and will have primary responsibility to coordinate appropriate receipt, inventory, long-term storage, and integrity of all biological specimens collected under the Common Protocol and specific RICC projects/protocols. Each country site will maintain the physical repository and input the ongoing collection of all samples (parent and Common Protocol). All biorepository specimens will be collected in accordance with standardized procedures as indicated in the RePORT International Laboratory Manual.

A. Country Biorepository Database Director/Manager

The Country Biorepository Director/Manager (or designee) will have primary responsibility and oversight of the country biorepository database. They will oversee the development and management of all processes related to specimen receipt, storage, shipment, and analysis. Major responsibilities may include, but are not limited to, the following:

- Provide overall leadership and collaboration to ensure operational success of the country biorepository database
- Serve as a liaison for RePORT investigators, collaborators, and other key stakeholders, and assist with all aspects of biorepository access and utilization, including for RePORT international projects
- Establish standard operating procedures (SOPs) to record/report in the biorepository database so samples from the RePORT country network can be stored with consistent validity
- Ensure appropriate/adequate biorepository conditions for the long-term storage of the Common Protocol specimens. This includes ensuring RePORT country sites have adequate space and power back-ups are made available to ensure specimen integrity
- Oversee the development of study-specific processes and plans to ensure that all protocol-required specimens are collected, received, and stored in accordance with the study protocol and GCP/Good Clinical Laboratory Practice (GCLP) guidelines
- Oversee the administration of biorepository specimens and maintenance of accurate data records
- Oversee the management of laboratories subcontracted to support the processing and analysis of samples as applicable
- Identify and implement methods to improve and streamline procedures for shipping, receiving, and tracking of biorepository samples
- Ensure the proper disposition, testing, and destruction of clinical samples in accordance with GCP guidelines and study-specific informed consent guidelines
- Ensure that appropriate policies are in place for access to and distribution of biorepository specimens
- Ensure the confidentiality of data and stored specimens

- Provide supervision and oversight of biorepository staff to ensure streamlined processes for biorepository specimen management
- Provide necessary equipment, software access for those Networks/Network sites using the biorepository platform recommended by the RICC, or an equivalent system
- Work with RICC Laboratory SOP group to activate consistent SOPs for laboratory conduct, processing, and storage of Common Protocol specimens, to ensure sample validity
- Coordinate, train, and manage activities of biorepository personnel in the use of the biorepository database platform, quality assurance, and reporting SOPs. This includes ongoing mentorship and guidance
- Work with the RICC and country network biorepository personnel in aspects of biorepository management, including:
    - Receipt
    - Inventory
    - Storage of samples
    - Use of FreezerPro® or equivalent software
    - Maintain an accurate inventory of biological materials stored within the biorepository.
    - Prepare and distribute quarterly inventory reports.
    - Develop and maintain biorepository SOPs and policies to ensure efficient biorepository operations.
- Manage all aspects of biological specimen management, including:
    - Specimen receipt
    - Registration
    - Processing
    - Verification
    - Storage
    - Shipment
- Establish and maintain key performance indicators and monitor performance to ensure best practices.

1.1.3.2. Laboratory and Operational Support to Country Networks/Country Sites

The country biorepository database operations, or the country network coordinating center, will also perform a central biorepository coordinating role in support of each of the country study sites. It will serve as the operations center responsible for the centralized procurement of specimen barcode labels, equipment (barcode scanner, printer, and software), Common Protocol specimen collection kits, and other items that are best obtained in a centralized manner. The coordinating role also includes ensuring that personnel are adequately trained and follow SOPs. This can be done via periodic audits.

A. Specimen Storage, Shipment, and Tracking Procedures

The RICC will be responsible for working with the country networks/country sites to coordinate the shipment and receipt of Common Protocol biorepository specimens being used for RePORT International/RICC protocols.

1.1.3.3. Use of Stored Specimens for Sub-Studies

The use of stored specimens for RePORT International projects or sub-studies will be governed by the RePORT Network Investigators. All requests for the use of specimens for analysis must be reviewed and approved by Network PIs, the EC, and relevant government agencies/sponsors. Specific procedures governing specimen and other data requests can be obtained from the EC.

1.1.4. Country Networks/Country Sites

The country networks/country sites will implement the Common Protocol at the site level. The RePORT country sites will recruit, enroll, and follow up on study participants, and collect data according to the procedures outlined in the Common Protocol and MOP. All staff members involved in the conduct of the Common Protocol serve an important function. The roles and responsibilities of some of the staff members are listed below. Specific position titles and responsibilities are merely suggestions that may be useful for protocol implementation. Apart from the Principal Investigator (PI) role, they may be revised as needed.

1.1.4.1. Principal Investigator

The PI at each country network/country site will be responsible for the overall conduct of research activities at the site(s). The PI will be expected to comply with the responsibilities defined by the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH E6, GCP: Consolidated Guidance), *[Enter country-specific guidelines/regulations, as applicable],* U.S. Code of Federal Regulations (CFR), and other applicable regulatory authorities. By signing the Investigator of Record Agreement (see MOP Section 3), the country network/country site PI agrees to:

- Personally conduct or supervise the investigations
- Conduct the study in compliance with the network’s current protocol, and only implement deviations from the protocol to prevent immediate harm to participants
- Obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval for the protocol, written informed consent form and assent form, any other written information to be provided to participants, and any other documents subject to IRB/IEC review
- Ensure that each participant is fully informed of all pertinent aspects of the study and provides written informed consent, when possible. Verbal or consent by fingerprint is acceptable
- Ensure that a qualified physician (Co-Investigator or Sub-Investigator) is responsible for all study-related medical decisions, and that adequate medical care is provided to all participants
- Ensure that all people assisting with the study are adequately informed about the protocol and their study-related duties and functions
- Promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to participants. No changes in the research will be made without IRB/IEC approval, except when necessary to eliminate apparent immediate hazards to participants
- Ensure the accuracy, completeness, legibility, and timeliness of data recorded in the study paper case report forms (CRFs) and eCRFs (database screenshots), and in all required reports
- Ensure study participant confidentiality by providing for the safe and secure storage of research records with limited access to study personnel
- Ensure that the country network/country site maintains financial management consistently with best practices
- Permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authorities, where required

In addition, the PI should routinely monitor the site's study progress in accordance with the quality assurance (QA) and QC procedures detailed in a site-specific Clinical Quality Management Plan (CQMP); see MOP Section 3 for details.

1.1.4.2. Study Coordinator

While the PI is responsible for all the activities of the country network/country site. The PI may delegate the following tasks associated with the conduct of the study to the study coordinator:

- Assist the country network/country site PI with the organization and coordination of study activities at the site, including logistical support and staff training
- Prepare the regulatory documentation needed for site registration and ensure that continuing review is completed in accordance with the IRB/IEC policies
- Ensure that the study is conducted in compliance with the current protocol
- Assist the country network/country site PI with the coordination and supervision of the contact, screening, and recruitment of study participants
- Ensure that informed consent has been obtained from the study participant prior to the initiation of research-related activities
- Schedule tests and appointments for study participants within the appropriate timeframes
- Identify abnormal laboratory test results and report all abnormal findings to the country network/country site PI
- Complete CRFs and enter data into the study database as required, and retain original source documents in the participant notebook where required
- Maintain source documentation for each study participant
- Respond to data clarification requests in a timely manner
- Maintain files for all IRB/IEC correspondence and regulatory documentation
- Contact the Common Protocol Help Desk, as appropriate, with questions regarding the conduct of the study
- Oversee data QA/QC at the site, and receive and respond to QC reports

1.1.4.3. Data Manager

The Site Data Manager plays a key role in the conduct of the study at each country network/country site. The Data Manager is responsible for ensuring the collection, quality, and transfer of Common Protocol data to the DMC. Once enrollment begins, the Data Manager ensures that data are collected, validated, complete, and consistent. The Data Manager liaises with country network/country site staff, collecting data and other data providers (e.g., the DMC and the Central Biorepository Database), and ensures that all such data are transmitted securely and are consistent with other data collected in the study. At the completion of the study, the Data Manager ensures that all data expected to be captured have been accounted for and that all data management activities are complete.

Major responsibilities of the country network/country site Data Manager may include, but are not limited to, the following:

- Assist with the setup and testing of Common Protocol data transfer processes to the DMC
- Develop/oversee the development of the country network/country site's data quality management plan and data management SOPs

- Oversee the FreezerPro® (or equivalent software) setup, use, and data quality at the country network/country site
- Oversee/perform CRF review
- Oversee/perform data entry
- Oversee/perform database queries
- Oversee/perform data cleaning
- Oversee/write and implement basic data validation checks
- Oversee/perform data audits
- Oversee/conduct manual reviews of data
- Ensure data completeness
- Respond to data queries from the DMC
- Oversee/review data discrepancies and contact data collection staff for resolution

2. HUMAN SUBJECTS CONSIDERATIONS

2. HUMAN SUBJECTS CONSIDERATIONS

This chapter provides information on human participants' protection and guidance on obtaining informed consent from potential participants for the RePORT International Common Protocol. Country networks/country sites must give serious consideration to the ethical concerns of participants, safeguard their rights, and protect their confidentiality.

2.1. Applicable International, National, and U.S. Regulations and Guidelines

All RePORT sites participating in the Common Protocol must be in compliance with both their national and U.S. regulations applicable to research involving human participants, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and consistent with OHRP's Federal Wide Assurances policies if receiving funds from U.S. sponsors. Please see the OHRP web page "Register IRBs & Obtain FWAs." Should international, national, and U.S. regulations or guidelines differ, the more restrictive regulations or guidelines will apply.

The ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting of trials that involve human participants. The objective of ICH GCP is to provide a unified standard to facilitate the mutual acceptance of clinical data by regulatory authorities in different jurisdictions. Compliance with this standard provides public assurance that the rights, safety, integrity, confidentiality, and well-being of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the research data are credible. Please refer to the most recent ICH GCP Guideline, dated January 6, 2025.

A good working knowledge of GCP principles is one of the most important learning objectives for all staff involved in the conduct of the Common Protocol. Good Clinical Practice and Human Subjects Protection (HSP) training should be completed prior to protocol initiation.

2.1.1. National Regulations and Guidelines

Each participating country will adhere to the regulations and guidelines that govern their location.

2.2. Informed Consent Process

This section provides instruction and guidance on obtaining informed consent from potential participants for the Common Protocol. The country network/country sites must give serious consideration to the ethical concerns of participants, safeguard their rights, and protect their confidentiality. This study is bound to the ethical principles espoused by the Declaration of Helsinki.

The consent process begins when a potential participant is initially contacted. Informed consent is a process of information exchange that, in addition to reading and signing the informed consent form (ICF)/assent form, may include participant recruitment materials, verbal instructions, question/answer sessions, and measures of participant understanding. The IRBs/IECs, Principal Investigators (PIs), and funding organizations all share responsibility for ensuring that the informed consent process is adequate. Thus, it is important that the ICF be the basis for a meaningful exchange between the PI or designee and the potential participant.

The PI is responsible for ensuring that informed consent is obtained from each participant before they participate in the research study, even when delegating the task of obtaining informed consent to another individual who is knowledgeable about the research. The IRB/IEC should, however, be aware of who will conduct the consent interview.

In addition to signing the ICF/assent form, the participant should enter the date and time of signature on the ICF, to provide verification that consent was obtained before the participant began participation in the study. If consent is obtained on the same day that the participant's involvement in the study begins, source documentation should indicate that consent was obtained prior to actual participation in the study (see section 2.2.4).

2.2.1. Elements of an Informed Consent Form

The Common Protocol Toolkit contains sample ICFs and assent forms for Cohorts A and B. The ICFs contain language for permission to store specimens for future use in research, including genetic studies. The ICF and assent forms may be used without further revision except for the required addition of specific site information. The ICFs can be revised to meet particular site needs.

All ICFs must be in compliance with ICH GCP as well as national and U.S. regulations, guidelines, and policies. Specifically, the document must contain the following statements:

- The study involves research, an explanation of the purposes of the research and the expected duration of participation, a description of the procedures to be followed, identification of any procedures which are experimental, and participant responsibilities
- A description of any reasonably foreseeable risks or discomforts to the participant
- A description of any benefits to the participant or to others which may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the participant
- A description of the extent, if any, to which confidentiality of records identifying the participant will be maintained and that notes the possibility that representatives from regulatory bodies, funding organizations, and/or designees may inspect the records
- For research involving more than minimal risk, an explanation as to whether or not any compensation and medical treatments are available if injury occurs; and if so, what they consist of, or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and participants' rights, and whom to contact in the event of a research-related injury to the participant
- Participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which they are otherwise entitled
- If and/or when the results of any required study testing will be made available to the participant
- Storage period of biological samples and how they may be used in the future. Participants should also be informed if the storage of biological specimens for future research is a requirement for study participation. If not, participants are to be given the option to refuse or to withdraw their consent regarding any storage of biological specimens. Furthermore, the ICF should clarify if these biological specimens will be shipped to and/or stored outside of the country where they were collected.

Note that all documents to be used in the informed consent process must be in a language and at a reading level that is understandable for the intended study population and must be approved by the IRB/IEC. Please refer to sections 2.2.7 and 2.2.8.

When appropriate, one or more of the following elements of information will also be provided to each participant:

- A statement that procedures may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which participation may be terminated by the investigator without regard to the participant's consent
- Any additional costs to the participant that may result from participation in the research
- Any anticipated payments to the participant for taking part in the study

- The consequences of a participant’s decision to withdraw from the research and procedures for orderly termination of participation by the participant
- A statement that significant new findings developed during the research, which may relate to the participant’s willingness to continue participation, will be provided to the participant
- The approximate number of participants involved in the study

In addition to these required elements, the ICF must also include the following:

- Protocol title and number
- Protocol date
- Protocol version number
- Name and address of the institution where the study is being conducted
- PI name
- Signature and date line for participant
- Signature and date line for the person obtaining consent
- Signature and date line for a witness to the consent process (if appropriate)
- ICF version number or version date

2.2.2. Ethical Considerations for Biorepository Specimens

Each participating RePORT country will have a unique set of rules and regulations governing the collection, storage, and use of biological specimens. Use of RePORT specimens will adhere to these regulations.

2.2.3. Revisions, Review, and Approval of Informed Consent Forms

The ICF must be revised whenever any of the following conditions apply:

- The protocol has been revised, and the amendment involves the number or frequency of study visits, evaluations given, or specimens obtained, changes in the risks associated with the treatment, or any new information that might affect a participant’s willingness to continue participating in the research
- There has been a change in the investigator or in any of the contact information
- An error or omission has been identified in the original/previous IRB/IEC-approved ICF

2.2.4. Documentation of Informed Consent

Source documentation should describe the informed consent process and include the following:

- The date and time; a notation of time is especially important when consent is obtained the same day that screening or enrollment occurs
- A description to substantiate that the process was not coercive
- Information about the study, including all available options, was provided in a language understood by the participant
- The participant was given an adequate opportunity to consider all available options
- The participant’s questions were answered
- The participant comprehended of the information
- That a copy of the ICF was given/offered to the participant

See section 2.2.7 for additional considerations for illiterate participants.

2.2.5. General Information about the Informed Consent Process

It is essential that each ICF be completed in compliance with ICH GCP and national and U.S. regulations and guidelines. Overall, the process of obtaining participant informed consent involves the following:

- Briefing the person about the study purpose, procedures involved, expected duration of the person's participation, and any potential risks and benefits associated with the study
- Explaining in simple terms to the person what their participation will require
- Explaining to the person their rights as a participant
- Explaining to the person that their participation is completely voluntary
- Reassuring the person that their information collected and/or used in this study will be kept private and confidential and will not be shared with people outside the study except for institutions that have regulatory oversight, or funding organizations or their designees that provided money to do the study and are required to review the study results
- Informing the person that they may withdraw from the study at any time without being penalized for withdrawal and with no impact on their clinical care or treatment
- Providing the name and contact information of a study staff member who participants can contact if they have any additional questions or concerns about the study
- Providing the name of an independent (non-study) representative of a local IRB/IEC whom participants can contact with questions about their rights as a participant, or if they feel they have not been treated fairly

The research staff member administering the consent will address all questions or concerns that the potential participant may have about the study, and must never attempt to pressure, persuade, or coerce them to join the study. In addition, for the Common Protocol, the participant will be asked if they are willing to have blood and sputum collected for storage and future use. Participants who are willing to have these specimens stored will be asked to provide written informed consent specifically for these activities.

Informed consent documents will be available in English as well as in the appropriate local languages to be determined by each country network/country site to ensure that each potential participant can be adequately informed about the study. The ICFs must contain all of the elements described in the ICH GCP Guidelines (ICH E6 R3, section 2.8.10), and in this chapter of the Manual of Operating Procedures (MOP).

After the PI or designee assesses the participant's or parent's/legal guardian's comprehension of the ICF, and that they voluntarily wish to participate in the study, the following procedures will be followed, in addition to those as required by the local IRB/IEC (see section 2.2.8 for assessing participant comprehension):

- The participant or their parent/legal guardian must sign the ICF (see section 2.2.7 for consenting illiterate participants or parents/legal guardians)
- The participant must receive a copy (signed or unsigned, per institutional requirements) of the ICF; the original signed ICF will be maintained in the country site study files
- The PI or designee obtaining consent must sign the ICF
- All dates and times must be entered by the people signing the ICF
- The dates and times the ICF was signed must precede any study-specific procedures
- Special procedures must be carried out for illiterate participants or parents/legal guardians, children, and other vulnerable populations (see sections 2.2.6, 2.2.7, and 2.2.9)

2.2.6. Minor Participant Assent

Children are considered a vulnerable population in clinical research due to their limited autonomy and intellectual maturity. U.S. Federal research regulations require that assent be obtained from children participating in research when the children are capable of providing assent (45 CFR Part 46 Subpart D). **Country sites/country networks should follow their local IRB's rules and regulations in obtaining assent from minors.** Sample assent forms for both Cohort A and Cohort B are included in the Common Protocol Toolkit.

2.2.7. Additional Considerations for Illiterate Participants

Participants or their parents/legal guardians who cannot read or write must go through the same informed consent/assent process as those who are literate; however, in these cases, the ICFs will be read to them in the participant's preferred language and per the institutional IRB/IEC policy.

An impartial witness must be present during the entire informed consent discussion. After the ICF and any other written information have been read and explained to the participant or their parent/legal guardian, they have orally consented to participation in the study and have signed or marked the ICF with their fingerprint, the witness will sign and personally date and record the time on the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and understood by, the participant or their parent/legal guardian, and that informed consent was freely given by the participant or their parent/legal guardian. The impartial witness must also write the participant's and parent/legal guardian's names in the designated spaces on the ICF to ensure the consent form can be linked back to the correct participant, or in accordance with the country site's IRB/IEC policies.

If the participant or parent/legal guardian cannot write the date and time next to their signature or fingerprint, the date and time must be left blank. In such cases, the study staff member administering the informed consent will note in the source document the reason a fingerprint was used and why the date and time were left blank.

2.2.7.1. Assessing Literacy of Potential Participants

International and federal statutes mandate that investigators obtain informed consent from a participant or parent/legal guardian. The information that is given to the participant or parent/legal guardian must be in a language understandable to the participant or parent/legal guardian. It is also important to ensure that participants can both read and understand what they agree to do and that participants are given sufficient time to read the ICF/assent forms.

There are several ways to assess literacy if a participant agrees to consider the study. The first and most basic way is to state that the ICF is 'X' pages long. The person obtaining consent should ask the participant if they need or prefer assistance in reading it. In addition, asking a participant to write their name on a separate piece of paper or read a simple three-to-four-word sentence may be another way to identify low-literate or illiterate participants. Another way to assess literacy is to review comprehension of the materials provided.

Observing a participant's behavior when given the ICF/assent form can be another way to identify a low literacy level. If consent pages are flipped too quickly and the form is signed hastily, this may indicate a low level or absence of reading comprehension. The person obtaining consent should engage the potential participant in conversation. Often, illiterate individuals appreciate an up-front offer to have the materials read to them. Should this be requested by the participant, an impartial witness must be present for the entire informed consent process.

2.2.7.2. Selection of Witnesses for Illiterate Potential Participants

The consent process involving an illiterate participant must be witnessed by an impartial individual. For informed consent purposes, an impartial witness is a person who is independent of the study, who is unlikely to be unduly influenced by people involved with the study, and who attends the informed consent process if the participant cannot read or write. During the consent process, if the potential participant is found to be illiterate, an impartial witness must be present during the entire informed consent discussion. The local IRB/IEC should be consulted to determine who is considered an impartial witness.

2.2.8. Assessing Participants’ Comprehension of Information Communicated

Throughout the consent process, the person obtaining consent should remain cognizant of the fact that the participant may not understand what is being said. During the consent process, one should speak slowly, use clear and simple explanations, and encourage questions periodically with prompts such as “Do you have any questions I can answer so far?” Once the information in the ICF is communicated, it is important to ascertain the participant’s comprehension of the consent document. One way is to ask the potential participant to explain the basic elements of the study such as “How many visits will you be required to attend for this study?” or “Why are we conducting this study?” Another way is to ask other questions not directly related to the research itself such as, “Should you decide to withdraw from the study, will your medical care here at the clinic be affected?” Be sure to allow adequate time to answer questions and for the decision-making process. If a potential participant seems hurried or unsure, encourage them to take the ICF home and review it with family members if desired.

2.2.9. Vulnerable Populations

Special precautions must be taken in the informed consent process when dealing with vulnerable populations (e.g., illiterate participants; pregnant women; pediatric populations; participants with visual, speech, or hearing impairments), and these precautions must follow the established IRB/IEC and local regulations. It is recommended that the sites have specific standard operating procedures (SOPs) for obtaining informed consent from vulnerable populations. Before administering informed consent to a vulnerable participant, the institutional guidelines for these cases should be clear and ideally have the written approval of the IRB/IEC, as required.

Pregnant women and children are eligible to be enrolled in the Common Protocol. The country sites will follow their local IRB/IEC policies for obtaining informed consent and assent from these individuals. At a minimum, assent will be obtained from children who are considered to be mature minors (e.g., from age 7 to 18 years) and according to local IRB/IEC policies. If the participant becomes of age to be consented as a mature minor or adult within the study participation period, study staff must follow the local IRB/IEC policy regarding assenting or consenting the participant. Sample consent forms and assent forms are located in the Common Protocol Toolkit.

2.3. Confidentiality

All biorepository samples, case report forms (CRFs), research-related records, and reports not considered source documentation must be coded with the participant identification (PID) number in order to preserve the participants’ confidentiality. The PID and the name of the participant must never be used in the same document, except for the PID logbook. All records, including CRFs and source documentation, must be kept behind two locked doors in a safe and secure area, preferably not at ground level or near sources of water or fire. Do not provide clinical information to non-study or unauthorized persons without the prior written permission of the potential participant or parent/legal guardian, unless the entities involved (e.g., the National Institutes of Health (NIH) and/or their designees, or other applicable funding organizations require it. All security measures for computer systems/electronic devices according to the country network/country site’s institutional policies must be followed by study staff in order to protect the participants’ confidentiality.

2.4. Participant Reimbursement for Study Participation

Participants may be compensated for their participation in this study to the extent approved by the IRB/IEC. Compensation cannot appear to exert undue influence to participate in the study. The offer cannot be so attractive that it may blind a prospective participant or parent/legal guardian to the risks of the study or impair their ability to exercise proper judgment. Although compensation is often monetary, participants may be offered compensation in forms other than money. This may include meals, transportation, free medical services, and gifts (e.g., toys), etc. Care must be taken to ensure that payment is commensurate with the risks, discomfort, and inconvenience that will be experienced. Any compensation to the participant must be approved by the IRB/IEC.

3. ADMINISTRATIVE AND REGULATORY REQUIREMENTS FOR PROTOCOL INITIATION

3. ADMINISTRATIVE AND REGULATORY REQUIREMENTS FOR PROTOCOL INITIATION

This chapter reviews the required procedures for the country networks/country sites to demonstrate compliance with the International Council on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines prior to protocol implementation. The documentation and submission requirements outlined in this chapter are intended for use by each of the country networks/country sites.

All country networks/country sites and U.S. partner institutions are required to comply with their own institutional guidelines, relevant partner institutional guidelines, and all other applicable regulations.

3.1. Administrative Requirements

The process to expand RePORT to include new countries or new sites is outlined in the RePORT International Bylaws. Country networks/country sites that are new to RePORT International must first complete a Country Implementation Plan and obtain approval from the RePORT Executive Committee as described in Section 8 of the RePORT International Bylaws.

Prior to study implementation for new and existing country networks/country sites, the country site Principal Investigator (PI) and designees must ensure that their facility and staff are properly prepared to implement the Common Protocol. All study-related procedures must be conducted in accordance with the Common Protocol and this MOP.

The following components must be completed before the Common Protocol can be implemented at a country site:

- The Common Protocol must be finalized with country network/country site-specific language added as required and approved by the local IRB/IEC. In some instances, a country network/country site will combine the elements of the Common Protocol into an existing country network/country site protocol.
- The MOP and case report forms (CRFs) must be approved and finalized at the country network/country site. The Common Protocol Toolkit includes directions on how to obtain a comprehensive set of Common Protocol CRFs with completion instructions.
- The local biorepository must be established and ready to receive clinical specimens for storage.
- The country site must have completed all study start-up activities and received approval for site establishment at the network and have all essential logistics and supplies in place for protocol implementation (e.g., country site procedures established, staff training completed, supplies procured, etc.). A sample Documentation of Training form is provided in Attachment 3-1.

3.2. Site Establishment Procedures

3.2.1. Regulatory and Essential Documents Binder

In accordance with the ICH guidelines, a number of essential documents that demonstrate compliance with the standards of GCP should be in place prior to protocol registration. The country site establishment documents should be filed in each country site's *Regulatory and Essential Documents Binder* (Attachment 3-2). Each country site is responsible for ensuring that the required documents are maintained in the regulatory binder (usually electronic). These regulatory and essential documents should be maintained in a secure area, accessible only to authorized individuals. The *Regulatory and Essential Documents Binder* should be updated to include renewed approvals, accreditations, and certifications as preceding documents expire. The *Regulatory and Essential Documents Binder* will contain the history of the study's essential documents and protocol approvals. The *Regulatory and Essential Documents Binder* for the Common Protocol should be maintained for the duration of the study and the period afterward specified by the IRB/IEC and funding organizations. The following documents will be maintained in this binder (either in physical form or electronically):

- Current and previous versions of the protocol

- IRB/IEC approval documentation for:
    - The Common Protocol (or the study protocol that incorporates the required Common Protocol elements)
    - Protocol amendment(s) including Clarification Memos (CMs) if applicable, Letters of Amendment (LOAs), and full version protocol amendments. See section 3.5.
    - Continuing reviews
    - All versions of the ICFs and assent forms (including all applicable translations and certificates of accuracy)
- Copy of the *Study Activation Letter* (if applicable)
- IRB/IEC correspondence

To facilitate organized and accurate maintenance of the *Regulatory and Essential Documents Binder,* it is permissible to:

- Maintain regulatory documents common to all studies in an organized and labeled central binder. Types of documents include:
    - CVs and medical licenses
    - Training certificates that are applicable across studies (e.g., HSP, GCP)
    - Laboratory certifications
    - IRB/IEC rosters
    - IRB/IEC assurances
    - Non-study-specific communications
- Maintain archived regulatory documents in an organized binder separate from the current regulatory documents. Types of documents include expired or no longer applicable:
    - IRB/IEC approvals (protocols, amendments, and consents)
    - Laboratory certifications
    - CVs
    - Medical licenses
    - Investigator of Record (IoR) Agreements

3.3. Country Site Study Activation

Activating a new country site is at the discretion of the participating RePORT country network under consultation with the RePORT EC. Site activation requires a set of country and RePORT-specific requirements to be met.This process is outlined in the RePORT International Bylaws.

3.4. Continuing Review

The country sites are responsible for resubmitting the protocol, ICF(s), assent form(s), and other supporting documentation to their IRB/IEC for continuing review at the frequency dictated by the IRB/IEC.

3.5. Protocol Clarifications and Amendments

Changes to a protocol or need for clarifications may occur after the final version of the protocol has been released to the country networks/country sites. There are three methods for clarifying or making changes to the Common Protocol: 1) Clarification Memo (CM), 2) Letter of Amendment (LOA), and 3) Full Version Protocol Amendment.

3.5.1. Clarification Memo

Provides further details or explanation of information that is already present in the protocol. The content of the CM has no impact on protocol design, participant safety, risk-to benefit ratio of study participation, or the informed consent/assent forms. A CM may also be used to correct typographical errors and minor inconsistencies, or to document administrative changes (e.g., changes to the protocol team). Country sites should submit CMs according to their local IRB/IEC guidelines.

3.5.2. Letter of Amendment

Specifies changes to a protocol that have minimal impact on participant safety and the risk-to-benefit ratio of study participation and involve relatively minor modifications of the protocol. An LOA may involve minor modifications of study ICFs/assent forms, which do not have significant impact on safety. An LOA may also be used to quickly communicate urgent participant safety or participant management issues that require prompt attention at the country sites while a full version protocol amendment is being developed. At the time of the preparation of an LOA, a decision is made whether a new protocol version will be required based on whether the changes are substantive in number and/or nature.

The country sites are required to submit the LOA and any amended country site-specific ICFs/assent forms to their IRB/IECs for review. LOAs may not be implemented until approval is received from the local IRB/IEC. The most recent approved protocol must continue to be implemented until the LOA is approved by the IRB/IEC. Once IRB/IEC approval is received, LOAs including any revised country site-specific ICFs/assent forms must be implemented immediately upon receiving all required IRB/IEC approvals unless the LOA specifies otherwise.

The country site may delay implementing an LOA when the IRB/IEC approved LOA states the protocol changes will be implemented once specific operational issues (e.g., training on new procedures in the LOA) are addressed. While waiting for operational issues to be addressed, new participants may be enrolled under the previously approved version of the protocol; and country sites will continue conducting the previously approved version of the protocol for already enrolled participants, as long as approved by the IRB/IEC, funding organizations, and the IOR. The IRB/IEC determination must be documented in writing and filed in the country site's regulatory binder.

3.5.3. Full Version Protocol Amendment (new protocol version)

Incorporates significant changes and results in the generation of a new protocol version number. The changes involve more than minimal impact on participant safety and risk-to-benefit ratio of study participation. A full version protocol amendment may or may not require a change to ICF(s)/assent form(s). All prior CMs and LOAs developed under the most recent protocol version are incorporated in the new protocol version.

The country sites are required to submit the amended protocol to their IRBs/IECs for review and approval. Full version protocol amendments may not be implemented until approval is received from the local IRB/IEC. The most recent approved protocol version must continue to be implemented until the amendment is approved by the IRB/IEC. Amendments including any revised country site-specific ICFs/assent forms must be implemented immediately upon receiving all required IRB/IEC approvals unless the amendment specifies otherwise.

The country site may delay implementing a full-version protocol amendment when the IRB/IEC approved amendment states that protocol changes will be implemented once specific operational issues (e.g., training on new procedures in the new version) are addressed. While waiting for operational issues to be addressed, new participants may be enrolled under the previously approved version of the protocol; and country sites will continue conducting the previously approved version of the protocol for already enrolled participants, as long as approved by the IRB/IEC. The IRB/IEC determination must be documented in writing and filed in the country site's regulatory binder.

3.6. Protocol Implementation, Accrual, and Retention Plan and Clinical Quality Management Plan

3.6.1. Protocol Implementation

The RePORT country network/country site will determine when all of the criteria have been met to initiate protocol implementation (IRB/IEC approvals in place, training completed, essential documents in regulatory binder, etc.). A *Study Activation Letter* may be drafted to document this, depending on site-specific requirements. Study procedures are directed by the protocol and guided by the MOP.

3.6.2. Recruitment, Accrual, and Retention Plan

Sites should develop recruitment, accrual, and retention plans. The study-wide accrual period begins on the first day of participant enrollment at any participating country site; country site-specific accrual periods begin on the first day of participant enrollment at the country site. The time from country site-specific study activation to the first day of participant screening, and the time from first screening to first enrollment, should be tracked. Participating country sites are responsible for establishing Common Protocol-specific recruitment, accrual, and retention standard operating procedures (SOPs), and for updating these SOPs as needed to meet accrual targets.

The scientific and ethical review process involves the consideration and approval of the number of participants to be enrolled in the study. Country sites will inform their IRBs/IECs of increases or decreases in their enrollment targets, in accordance with IRB/IEC requirements.

3.6.3. Clinical Quality Management Plan (CQMP)

It is recommended that each country site establish and implement a CQMP. This recommendation is to ensure:

- Proper planning for study implementation
- Compliance with the Common Protocol, MOP, regulations, IRBs/IECs
- Verification of the accuracy of data submitted to the data management center
- Identification of areas in need of corrective action and follow-up
- Avoidance of costly corrective action and duplication of effort
- Continuous quality improvement of study conduct and documentation
- Assurance of a constant state of readiness for site visits and external audits

A sample CQMP is available in Attachment 3-3 that may be used as a template for developing the country site’s plan, but it is not required that this template be used.

3.7. Participant Recruitment Materials

Recruitment materials (e.g., posted or distributed flyers, newspaper or magazine advertisements, announcements posted to websites or sent by email) intended to be seen by potential participants should not promise unreasonable benefits or give the impression of coercion. All advertising or recruitment materials must have local IRB/IEC approval before they can be used for the Common Protocol.

Informing colleagues about the Common Protocol and asking them to refer individuals for participation in this study is not considered advertising in this context. Only material to be viewed by potential participants must be reviewed by the IRB/IEC.

3.8. Supplies Needed for Protocol Implementation

The study coordinator or designee is responsible for ensuring that adequate supplies are available at the country site to begin protocol implementation.

Attachment 3-1

RePORT International Common Protocol Sample Documentation of Training Form

This form should be used and modified to document that the training requirements outlined in Section 5 of the RePORT International Manual of Operating Procedures were completed.

Country Site Name: ___________________________

Name of Staff: ___________________________

Position: ___________________________

Date Started on Project: (DD/MON/YYYY) ___________________________

Training Element	**Check if N/A**	**Date Completed**	**Signature***
Common Protocol – In-person training			
Common Protocol – Read protocol and acknowledged understanding of contents			
Case Report Form (CRF) Completion Instructions review and acknowledgement of contents			
Manual of Operating Procedures (MOP) review and acknowledgement of contents			
Chest X-Ray Reader Training			
Laboratory Procedures (specify)			
RePORT International Laboratory Manual			
FreezerPro®			
QuantiFERON®-TB Gold Plus (QFT-Plus)			
Clinical Quality Management Plan			
Site Standard Operating Procedures (SOPs) and other documents (specify)			
Other			

*Acknowledgement of participation in training and/or review and understanding of documents

Attachment 3-2

Sample Table of Contents for Regulatory and Essential Documents Binder

The following is a sample list of sections (divider tabs) that should be included in a Regulatory and Essential Documents Binder. In order to comply with GCP, each country site will be responsible for creating a binder which contains the below listed divider sections, or comparable sections, and corresponding items.

I. Protocol and Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
  a. IRB/IEC Roster
  b. IRB/IEC Federal Wide Assurance (FWA)
  c. IRB/IEC Correspondence, Approvals, and Continuing Review
  d. IRB/IEC-Approved Informed Consent Forms and Assent Forms
  e. IRB/IEC-Approved Participant Materials
  f. IRB/IEC-Approved Advertisement for Recruitment (if used)
  g. Protocol, Full Protocol Amendments (i.e., new protocol versions), Letters of Amendment, Clarification Memos
  h. Case Report Forms (CRFs)/Completion Instructions
  i. Investigator of Record Agreement
  j. Curriculum Vitae/Licenses
  k. Human Subjects Protection (HSP), Good Clinical Practice (GCP), and Good Clinical Laboratory Practice (GCLP) Training Documentation
  l. Protocol and other Training Documentation
  m. Financial Disclosures
  n. Job Descriptions
  o. Delegation of Authority/Master Signature Log

II. Country Site Visit
  a. Country site Support Visit Log
  b. Country site Support Visit Reports

III. Other
  a. Participant Screening and Enrollment Log
  b. Participant Identification (PID) Number List
  c. Laboratory Normal Ranges
  d. Laboratory Certifications and Accreditation
  e. Certification to Ship Dangerous Goods (e.g., International Air Transport Association (IATA))

Attachment 3-3

Sample Clinical Quality Management Plan (CQMP)

(SAMPLE ONLY. The template below is provided for your convenience as an example of how this information may be provided. Frequency/percentage of reviews and types of tools/reports used should be selected to meet the specific needs of the country site.)

Country Site Name: ______________________________

Section I: Responsibility

Mary Brown, MD, Principal Investigator, is responsible for the CQMP at: ________________________.

John Smith, RN, Study Coordinator, has been designated by Dr. Brown to be responsible for the implementation of the CQMP.

Section II: Key Quality Control (QC) Staff

Bill Thomas, Data Manager, is responsible for the day-to-day QC activities, with support from other data personnel.

Section III: Key Quality Assurance (QA) Staff

Sara Johnson, RN, is responsible for QA activities at the site.

Section IV: Quality Management (QM) Activities and Tools

Quality Control (QC)

The following activities and tools will be utilized in the QC process:

1. Error Correction Reports from the data management center will be reviewed by the Data Manager, who will immediately bring any errors identified to the attention of the appropriate site staff for correction. Errors will be corrected within 2 business days of identification.
2. Data Entry and Transmission Reports will be reviewed by the Data Manager to ensure that transmitted data was successfully entered into the database. Errors will be brought to the attention of the person responsible and corrected within 1 business day of identification.
3. Error Tracking Logs will be completed by the Data Manager. This log identifies and tracks categories of Case Report Form (CRF) errors. This information will be aggregated and reported to the site staff as a whole at weekly meetings.
4. Data staff will review 100% of CRFs prior to data entry for completeness, to ensure proper dating and signing, etc.

Quality Assurance (QA)

The following activities and tools will be utilized in the QA process:

1. The Chart Review Tool is utilized for participant-specific chart review. It is inclusive of all key indicators for QA review as listed in Section V below.

2. The Regulatory Review Tool is used for quarterly review of regulatory documents, including Safety Report submission, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals and communications, etc.
3. Monthly Activity Reports are protocol-specific summaries of QM activities that are shared with the site staff at monthly meetings.
4. Country Site Support Visit Reports are utilized as a QA tool, checking for any adverse trends or problems. These reports will be shared during staff meetings.

Section V: Key Indicators

These indicators are part of the chart review:

1. Informed consent forms and processes
2. Eligibility criteria
3. Missed visits, tests, and procedures
4. TB treatment administration
5. Protocol endpoint identification

Section VI: Review Priorities

QA and QC are ongoing activities. Monthly QA reviews will consist of 10%, at a minimum, of the clinic records, altering existing open protocols to ensure review of all active protocols over the course of the year.

Priorities will be in the following order:

1. New Staff: 100%, and no less than 5, of all visits completed by new staff will receive a QA review until competency is determined.
2. New Protocols: The first three records for a new protocol will receive a QA review.
3. Complex Protocols: Based on recommendations of the Principal Investigator (PI) and/or Study Coordinator, complex or large protocols may be targeted for an early or more thorough review.

Section VII: Correction Process

Once a problem has been identified by analysis of the QA or QC findings, it will be discussed with the site staff at the next monthly meeting. The root cause of a recurrent problem will be identified, and actions will be taken to correct the problem based on the input from the site staff. These actions may include but are not limited to changing a process or form; training; or reassigning a task. Any adverse trend will be re-evaluated to assess the effectiveness of the corrective action.

Section VIII: QM Results Reporting

Documentation of QM findings will include:

1. Date of review
2. Name of reviewer
3. Participant Identification (PID) Number
4. Items reviewed

5. Findings/results of review
6. Time period covered by review

Additionally, there will be a monthly report prepared by the Data Manager, which will include both the protocol-specific and site-specific summary of QM findings for the month. When monitoring reports are received, these findings will be included in the summary report. This report will be shared with site staff at the monthly staff meeting. Overall QA and QC findings, corrective actions, and follow-up actions will be discussed at staff meetings.

Section IX: Staff Training

All new staff will have a competency-based orientation using the tools and forms from the site standard operating procedure (SOP) manual. A competency checklist will be completed by both the new staff member and site-designated training mentor. Orientation to relevant policies and procedures will occur. Training will be documented, signed, and filed in the study Regulatory Binder.

Section X: Revision/Evaluation/Reporting

There will be an annual staff meeting at which an analysis of the findings and activities of the previous year is undertaken. At this meeting, it will be determined if any changes are to be made to the CQMP. Additionally, Dr. Brown will prepare an annual evaluation of the CQMP and its activities to be submitted to the Site Performance Committee (SPC), utilizing the SPC-specific format.

Submitted by: Mary Brown, MD, Principal Investigator (Example)

Signature: ___________________

Date (DD/MON/YYYY): ____________________

4. COMMON PROTOCOL OVERVIEW

4. COMMON PROTOCOL OVERVIEW

This chapter provides details pertaining to recruitment, screening, enrollment, and follow-up study visit activities that are not included in the protocol document. Country network/country site staff is encouraged to contact the RePORT Support Team with any questions or requests for clarification regarding recruitment, screening, enrollment, and follow-up visit procedures. The Common Protocol can be found on the RePORT International website.

The purpose of the RePORT International Common Protocol is to establish a biorepository with an associated database of well-characterized specimens and standardized data for future tuberculosis (TB) research.

A uniform schedule and methodology have been designed for collecting blood and sputum specimens from participants in each cohort. It is recommended that the country networks/country sites integrate the uniform schedules into their respective parent protocols for harmonization across networks.

In Cohort A, data and biospecimens will be collected at three to five visits:

- Baseline
- Month 2/8 weeks (-2 weeks/+2 weeks)
- Month 6/26 weeks (-4 weeks/+6 weeks) (if EOT does not fall within the Month 6 visit window)
- End of Treatment (TX)
- If applicable, at the time of apparent or actual treatment failure, TB relapse(s), or withdrawal (Treatment Failure, Relapse, or Withdrawal Evaluation (TX F/R/W) Visit)

Additionally, participants will complete a month 12 visit/52 weeks call (-4 weeks/+6 weeks) in which participant status/medical history will be obtained.

In Cohort B, data and biospecimens will be collected at the following visits:

- Baseline
- At the time of apparent or actual development of active TB (TB Activation Evaluation Visit)

Additionally, information about each participant’s health status will be collected to actively identify participants who develop active TB during the following visits:

- Month 6/26 weeks (-4 weeks/+6 weeks)
- Month 12/52 weeks (-4 weeks/+6 weeks)
- Premature discontinuation visit: 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.

4.1. Implementation and Oversight

This section reviews procedures to guide sites in recruiting participants and performing study-related clinical activities in a standardized manner. All aspects of the study visits, including clinical and laboratory evaluations, and biospecimen collection for the Local Biorepository, must be conducted according to the *Common Protocol Schedule of Events* in Sections 4.5 (Cohort A) and 5.5 (Cohort B) of the Common Protocol.

Every attempt should be made to conduct each study visit in a setting conducive to participant confidentiality. Study staff should be friendly and non-threatening to help establish a positive rapport with participants.

4.1.1. Screening and Enrollment Procedures

4.1.1.1. Recruitment for Cohorts A and B

Country network/country site staff will ask all individuals at the time they are being screened whether they would be interested in enrolling in Cohort A (TB index cases) or Cohort B (household contacts/close contacts). If they are interested, the country network/country site staff may begin the informed consent process for this study. It is important that the recruitment process begin as early as possible to increase the likelihood that eligibility criteria are met, especially for Cohort A participants.

4.1.1.2. Screening Visits for Cohorts A and B

At the Screening Visit, a signed informed consent form (and assent form where appropriate) must be obtained prior to performing any screening evaluations or procedures that are not a part of routine clinical care. Refer to Section 2 of this document for details regarding the informed consent process.

B. Screening and Enrollment Log for Cohorts A and B

The Principal Investigator (PI) or designee is required to complete the *Study Screening and Enrollment Log* (Attachment 4-1) for all individuals who are screened for the Common Protocol, regardless of whether they are enrolled. The log records the age, birth sex, race/ethnicity, consent date, screening date, participant identification (PID) number, and enrollment date, if applicable. If the individual does not provide consent, is ineligible, or is eligible but not enrolled, the reason will be recorded if this information is available.

C. Screening Evaluations for Cohorts A and B

The PI is responsible for ensuring that all eligibility criteria are met prior to enrolling a participant into the Common Protocol (refer to the Common Protocol Section 4.2 for Cohort A and Section 5.2 for Cohort B for inclusion and exclusion criteria). During the Screening Visit, all eligibility criteria must be documented and verified, including consent obtained, before the baseline evaluations are initiated. Each inclusion and exclusion criterion must be addressed in the source documents, including statements that exclusion criteria are not present. Documentation of pertinent negatives, such as “participant has not received more than a week of any anti-TB drugs within the past 30 days before provisional enrollment,” is as important as the documentation of meeting inclusion criteria. A signed and dated eligibility worksheet may be used to assist in this process and kept in the participant’s study records as source documentation. Refer to the *“1A - Inclusion and Exclusion Criteria”* and *“1B - Inclusion and Exclusion Criteria”* CRFs that should be used at the Screening Visit for Cohorts A and B, respectively. In addition, supporting documentation is required to verify that participants met inclusion and exclusion criteria, e.g., laboratory reports and documentation of medical histories in the participant’s chart.

Definitions of the TB signs and symptoms in the protocol, Section 4.2.1, are provided below:

Fever	If measured by a thermometer, greater than 38°C; if not measured, self-reported fever is accepted
Hemoptysis	Coughing up blood or blood-tinged sputum
Persistent Cough	Cough lasting about 2 weeks or longer
Pleuritic Chest Pain	Sharp chest pain that gets worse with deep breaths or coughing
Night Sweats	Excessive perspiration, which can soak sleepwear and bedding
Fatigue	General lethargy and inability to perform activities of daily living efficiently or at all

For a list of required clinical and laboratory evaluations, refer to the Common Protocol. For information regarding case report form (CRF) completion, refer to country-specific documentation with instructions on CRF completion.

At the Screening Visit, Cohort A participants must be asked whether they are willing to have an HIV test. To be eligible for participation in the Common Protocol, all participants 18 years of age and older are required to have an HIV test by the end of the Month 2 Visit study window. If an HIV test is not completed within this timeframe, the participant will be discontinued from the study. Children younger than 18 years of age are required to have an HIV test only if they were born to an HIV-positive mother (see protocol Section 4.2). HIV counseling and testing will be done through standard of care testing. **NOTE:** Follow country guidelines regarding HIV testing.

4.1.1.3. Contact Information for Cohorts A and B

After the informed consent form is signed, study staff will collect contact information from the participant. Contact information will be used to: 1) remind participants of upcoming study visits; 2) follow up with participants if they missed a study visit; and/or 3) follow up on participants' health status, as needed.

If not already collected, participants will be asked to provide a current home address, working phone number, or other contact information (e.g., email address) through which they can be reached for study purposes only. They will also be asked to provide valid contact information for a family member and/or friend who can be called in the event the participant cannot be reached. Participants will be asked if messages can be left at the numbers provided, and their response will be documented so that all country network/country site staff members know whether messages may be left. The country network/country site staff will not leave messages unless expressly permitted to do so by the participant. If permission is given to leave messages, country network/country site staff will assure participants that messages left with a family member or friend will only ask that the participant contact study staff and will not include any protected health information or information related to study participation. (Refer to Attachment 4-2 for a *Sample Contact Information Form*.)

4.1.1.4. Enrollment Procedures for Cohorts A and B

NOTE: A complete set of CRFs aligned with the Common Protocol Version 2.1 can be obtained at reportinternational.org. The CRFs that may be required for each study visit, as per the Common Protocol, are listed in Attachment 4-3A (Grid Cohort A) and Attachment 4-3B (Grid Cohort B). Please review the Event Grids and complete the appropriate CRFs for each Study Visit. Additional details are provided below.

Once eligibility is verified and documented, participants may be enrolled in the study by completing a Baseline Visit. Screening and Baseline Visits may occur on the same day as long as it has been verified that all eligibility criteria are met. If participants return for the Baseline Visit on another day, it is important to re-verify that participants are still eligible for the study prior to completing baseline evaluations, e.g., if by the time a Cohort A participant returns for the Baseline Visit, he/she has had more than one week of anti-TB medication, he/she is no longer eligible to be enrolled into the study. In Cohort B, if a participant returns for the Baseline Visit, and has developed signs or symptoms of active TB and subsequent chest x-ray (CXR) or sputum culture results are not available to rule out active TB, then enrollment must be delayed until active TB has been ruled out. If TB is confirmed, he/she is no longer eligible to be enrolled in the study; however, this individual may be eligible for Cohort A. Refer to the protocol for required clinical and laboratory evaluations.

4.1.1.5. RePORT International's Laboratory Guidelines

The RePORT International Consortium requires that all country networks/country sites develop a comprehensive laboratory manual of procedures (MOP) before initiating enrollment under the Common Protocol. The network/site lab MOP must meet the minimum standards listed in the RePORT Key Guidelines for the TB Laboratory and RePORT Key Guidelines for the Immunology Laboratory.

4.1.2. Clinical and Laboratory Evaluations for Cohort A Participants

This section provides guidance on the implementation of study visit evaluations for Cohort A participants. All evaluations for each study visit must be conducted according to the Schedule of Events in the protocol (Section

4.5 for Cohort A) and documented. Documentation should state whether the evaluations were completed and, if not, the reason why.

4.1.2.1. Demographic Information for Cohort A

Please see *DM - Demographics Cohort A* CRF.

- **Date of birth (DOB):** Record the DOB as reported by the participant and/or parent/legal guardian. Record as much information as possible (i.e., day, month, and year), but at a minimum, the birth year should be recorded. If the birth year is unknown, then record the participant's estimated age in years.
- **Sex at birth:** Record the participant's sex at birth, as reported by the participant and/or parent/legal guardian. If a participant currently identifies as transgender, list the biological sex at birth.
- **Dwelling location:** Country network/country site staff should decide whether the dwelling location qualifies as "City", "Town/Suburb", "Rural (countryside)", or "Other" based on local definitions.
- **Household income:** Ask the participant and/or parent/legal guardian the approximate total monthly income for his/her household. This figure should include the total amount from all wage earners and income sources. For example, if there are three people who work in the household, indicate the sum of those incomes from all three wage earners. Also, consider income from the pensions of household members. If a wage earner currently has TB and is unable to work, calculate the monthly income based on his/her income prior to illness. Definitions of terms related to household income are provided below:

Wage earner	Any person who contributes to the income of the household.
Member of household	Any person dependent on income who is a part of the household, including wage earners and non-wage earners.

- **Race/Ethnicity:** Record information based on country-specific guidelines.
- **Other demographic information** collected on the *DM - Demographics Cohort A* CRF includes marital status, religion, educational level, and number of household members.
- **Household tracking:** In order to link Cohort A and Cohort B household members, the *HT - Household Tracking Cohort A* CRF should be completed.

4.1.2.2. Medical History for Cohort A

A medical history is required at each study visit to determine and confirm study eligibility, collect information that may have an impact on the disease process, and assess the participant's health status over the course of the study. Note that some questions may be of a sensitive nature, such as HIV status, therefore, it should be explained to participants in advance why certain questions are being asked in the context of TB diagnosis, treatment, and progression.

At the Baseline Visit, the participant will be asked whether this is a new case of TB or a relapsed case, and specific questions related to the previous treatment. Please see *TH - Tuberculosis (TB) History* CRF.

- **TB Treatment History:** Country network/country site staff will ask participants about their TB treatment medication history. At the Screening Visit, country network/country site staff must ascertain whether participants have taken any medication with anti-TB properties for more than 1 week within 30 days before the Baseline Visit. If participants had more than 1 week of any medication with anti-TB properties by the Baseline Visit, they are not eligible to enroll in the study.

- **Concomitant Medications:** CRU staff will ask participants to report non-study medication and concomitant medications/therapies taken during the study. Please see *CM - Concomitant Medications* CRF.
- **General Medical History and Physical Exam:** The following information will be captured on the *PE - Physical Exam and Medical History/Diagnoses* CRF.
  - Date of physical exam
  - Height: Height (or knee height, if participant is unable to stand) in accordance with the country network/country site's standard operating procedure (SOP) to ensure that reported values have been measured in a standardized manner. See Attachment 4-4. Height will be measured at the Baseline Visit for all participants. At subsequent visits, height (or length) is only measured for participants 21 years of age and younger.
  - Weight: Weight will be measured at every visit by country network/country site site staff using the same scale at each study visit (if possible) in accordance with the country network/country site's SOP to ensure that reported values have been measured in a standardized manner. If there is more than one scale at the clinic, it is recommended the site staff note which scale was used at each visit.
  - Diabetes status
  - HbA1C test results
  - COPD status
  - Other comorbidities
  - CBC results
  - BCG vaccination/scar
  - Pregnancy test results

NOTE: Refer to Common Protocol Section 6, Off-Study Criteria for Cohorts A and B, for minimum baseline specimen collection requirements before participants have had more than one week of anti-TB medication.

- **TB Treatment Medications and Adherence:** At the Baseline Visit, a participant's prescribed anti-TB medications will be recorded on the *PH - TB Prophylaxis and TB Treatment History* CRF. At each follow-up visit, country network/country site staff should review the participant's country-specific document that will be used to track anti-TB drug administration, e.g., directly observed therapy (DOT) card], to verify whether there have been any changes to their treatment regimen. If their treatment card is not available, ask them about any changes to their treatment regimen and record this in the participants' source documents and on the *PH - TB Prophylaxis and TB Treatment History* CRF.

At follow-up visits through the End of TX Visit, country network/country site staff will review participants' country-specific document that will be used to track anti-TB drug adherence, e.g., DOT card, to evaluate adherence. If this document is not available, country network/country site staff will document the number of doses participants were supposed to take based on the previous study visit date, the current study visit date, and the prescribed treatment regimen. Site staff will then ask participants the number of doses missed, if any, since the previous visit. Based on the number provided, country network/country site staff will record the number of completed doses since the last visit. This information will be recorded in the source documents.

- **Testing for TB Infection:** There are 2 types of tests to detect the presence of *M. tuberculosis* infection – the Mantoux Tuberculin Skin Test and Interferon Gamma Release Assay. Use the appropriate CRF for the test used.

  - **Mantoux Tuberculin Skin Test (TST):** Record the most recent TST result with measurement, if done as part of standard of care, and a documented test result is available on the *TT - Tuberculin Skin Test* CRF.
  - **Interferon-Gamma Release Assay (IGRA):** Whether done as part of standard of care or as part of the common protocol, record IGRA results on the *IG - Interferon Gamma Release Assay (IGRA)* CRF.
- **HIV History:** The *HI - HIV Status* CRF should be used to document whether an HIV test was conducted and whether the participant was previously diagnosed with HIV. Self-reported information is adequate, and it is not expected that they will provide supporting documentation of their diagnosis. If they have been diagnosed with HIV, ask their diagnosis date and whether they are currently on antiretroviral therapy (ART). If they are taking ART, ask them for the start date of their current prescribed regimen. If the exact dates of diagnosis and start date of their current ART regimen are unknown, ask participants to estimate the year. The *AT - Antiretroviral Therapy* CRF should be completed to capture this information.
- **Current Pregnancy/Birth Outcome Status:** Document information as provided by participants on the *PO - Pregnancy/Birth Outcome* CRF. If medical records are readily available, use these to determine gestational age. If medical records are not available, estimate the gestational age as provided by participants. If there were multiple births, complete a separate CRF for each fetus/newborn. Participants will be asked about pregnancy at each follow-up visit, including any pregnancy outcomes that occurred in between visits. **NOTE:** Follow Institutional Review Board inclusion criteria as well as clinical recommendations for treatment and monitoring during pregnancy and postpartum.
- **Tobacco Smoking History:** The Common Protocol is interested in participants' smoking history in pack years and, if a former smoker, the time since they quit smoking. Definitions of terms related to smoking history are provided below. The *SU - Substance Usage* CRF should be used to document tobacco smoking history.

Term	Definition
Current Smoker	Participants who smoked 100 cigarettes or other types of tobacco (e.g., bidis, cigars, etc.) or 10 hours of hookah in their lifetime and currently smoke every day (daily) or some days (non-daily).
Former Smoker	Participants who have smoked at least 100 cigarettes or other types of tobacco (e.g., bidis, cigars, etc.) or 10 hours of hookah in their lifetime but say they currently do not smoke.
Never Smoker	Participants who have never smoked a cigarette or other types of tobacco (e.g., bidis, cigars, hookah, etc.) or who smoked fewer than 100 (or 10 hours of hookah) in their entire lifetime.

- **Alcohol Consumption History:** The three questions related to alcohol consumption will be asked of the participants during the Baseline Visit (taken from the World Health Organization's (WHO) Alcohol Use Disorders Identification Test (AUDIT-C).) The *SU - Substance Usage* CRF should be used to document alcohol consumption history. Before asking participants these questions, it is important to tell them the purpose of the questions and to assure them that responses will be confidential. Ask the questions as they are written and, in the order, indicated. This will allow for better comparability between results obtained by different interviewers from different participants. After reading the question, provide the response categories given for each question. If participant responses are ambiguous or evasive, the interviewer may need to repeat the question and response options for the participant. It may be difficult for participants to choose an option because they may not drink on a regular basis. For example, a participant may go through periods of increased drinking and at other times does not drink as much, making it difficult to characterize the “typical” drinking sought by the question. In this case, record the amount of drinking for the heaviest drinking period, making note of the fact that this may be atypical in the source documents.

- **Illicit Drug Usage History:** Please report history of illicit drug use on the *SU - Substance Usage* CRF.

4.1.2.3. Clinical Evaluations for Cohort A

- **Chest X-Ray (CXR):** CXRs (either digital- or film-based chest X-rays) will be conducted per protocol requirements. The results should be documented on the *CX - Chest X-Ray* CRF. If CXRs are completed as part of the standard of care within the protocol-specified timeframe, the CXR does not need to be repeated for the Common Protocol. Pregnant women are not required to have a CXR for the Common Protocol; however, if completed as part of standard of care, the results will be recorded on the *CX - Chest X-Ray* CRF.

  All CXR images will be labeled with:

  - PID
  - Study visit type (e.g., Baseline, Month 2, End of TX, TB Activation Evaluation)
  - Date of the CXR

  All personal identifying information must be removed from the CXR image, including name, address, DOB, and any identifier other than the Common Protocol PID that could link the image to the participant.

- **Eligibility Confirmation:** At the two-month follow-up visit, country network/country site staff must check to see if enrolled participants meet confirmatory inclusion criteria (see protocol Section 4.2.3). To remain in the study, participants must have 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. If participants do not meet eligibility criteria within two months of the Baseline Visit, or it is unknown whether or not they meet confirmatory inclusion criteria during this timeframe, they will be discontinued 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.

- **Assessment of Other Psychosocial Factors:** Investigators and/or designees must use their best judgment when assessing a potential participant’s capacity to provide informed consent and adhere to study requirements. For example, if at the time of informed consent an individual’s speech is slurred or the individual is stumbling because of alcohol consumption, then they may not be able to provide true informed consent but may return at another time to go through the informed consent process. If, on the other hand, they are intoxicated on the second or third attempt at informed consent, the team may well decide that the person is unlikely to be able to ever fully comply with study requirements and decide not to try further enrollment attempts.

4.1.2.4. Clinical Laboratory Evaluations for Cohort A

The following specimens will be collected for local laboratory testing at specific timepoints as described in the Common Protocol section 4.3: (1) blood for a complete blood count (CBC) and lymphocyte count, Hemoglobin A1C (HbA1c), HIV, and CD4+ cell count (if HIV-infected) and (2) sputum for an AFB smear, culture, Gene Xpert, and drug sensitivity testing (DST). Country network/country site staff will review the participant’s medical chart and research records to determine if the blood tests were performed as standard of care. Sputum must be collected regardless of whether a sputum specimen was collected as standard of care. Refer to RePORT Key Guidelines for the TB Laboratory and RePORT Key Guidelines for the Immunology Laboratory and institutional SOPs for specimen collection procedures. The RePORT Key Guidelines can be found in the Common Protocol Toolkit. Please document all tests in the appropriate CRFs as per the RePORT International Common Protocol Form Event Grid Cohort A Appendix 5-3A.

The country network/country site staff is encouraged to provide the participant with abnormal laboratory or clinical reports to take to their primary care provider so that they may receive appropriate follow-up care.

4.1.2.5. Research Laboratory Evaluations/Biorepository Storage for Cohort A

Blood will be collected to obtain plasma for storage in the biorepository at specific timepoints as described in the Common Protocol section 4.3. If blood collection volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the local Institutional Review Board or Independent Ethics Committee (IRB/IEC) guidelines, or country-specific or other guidelines, as applicable, specimens will be prioritized as outlined in the “RePORT Key Guidelines for the Immunology Laboratory.” A baseline sputum specimen for MTB isolate storage will be collected.

Country network/country site staff should complete the *SS - Specimen Storage* CRF to document all specimens being stored in the biorepository as per the RePORT International Common Protocol Form Event Grid Cohort A Appendix 5-3A.

It is important that country network/country site staff members are trained and knowledgeable about specimen collection, temporary storage, and transportation requirements to ensure that the specimens arrive in good condition at the country network/country site’s processing laboratory and are viable for long-term storage and future use. Refer to the “RePORT Key Guidelines for the TB laboratory” and “RePORT Key Guidelines for the Immunology Laboratory” found in the Common Protocol Toolkit.

4.1.2.6. Modified MRC Dyspnea Scale

Cohort A participants will be asked to complete the Modified MRC Dyspnea Scale at the Baseline Visit as well as at the Treatment Failure/Relapse/Withdrawal Visit. Please document the participant’s response in the *MD - Modified MRC Dyspnea Scale* CRF.

4.1.3. Clinical and Laboratory Evaluations for Cohort B Participants

This section provides guidance on the implementation of study visit evaluations for Cohort B participants. All aspects of participant visits, including clinical and laboratory evaluations and sample collection, must be conducted according to the Schedule of Events in the protocol (Section 5.5 for Cohort B). Screening, Baseline, and TB Activation Evaluation Visits must occur in-person, while follow-up visits may be conducted by phone.

4.1.3.1. Demographic Information for Cohort B

Demographic information: See MOP Section 4.1.2.1. The *DM - Demographics-Cohort B* and *HT - Household Tracking-Cohort B* CRFs should be completed at the Baseline Visit.

4.1.3.2. Medical History for Cohort B

A medical history will be obtained at Screening and Baseline Visits. At subsequent study visits, participants will be asked questions to determine whether they have developed active TB.

Screening evaluations will be conducted to ensure that individuals meet the eligibility criteria outlined in Common Protocol 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 Attachment 4-1).

- **Significant Recent Exposure:** At the Screening Visit, the country network/country site staff will assess whether or not the potential participant has had significant recent (within the past 6 months) exposure 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 (e.g., congregate setting exposures) are eligible. The purpose of selecting people with recent exposure is to enrich the Common Protocol sample with people most likely to progress from TB infection to active disease, and this is most likely to occur soon after initial infection.

There are multiple factors to consider when determining “significant exposure,” such as:

  - Characteristics of the index case (IC) as well as the contact case (e.g., immune status, age, comorbidities)
  - Quality of exposure: Intense (e.g., living together) or casual (e.g., public transportation)
  - Size and airflow of the enclosed space (e.g., large room with many windows, small room with no windows)
  - Gradation of exposure (e.g., sharing the same bed, living in the same compound)

As there is no uniform definition for “significant exposure,” investigators and/or designees at each country network/country site are expected to use their best judgment to determine whether or not significant exposure occurred. Examples of significant exposure include:

  - Sleeps under the same roof as the IC, at least 5 days per week
  - Shares at least 1 meal per day with the IC, at least 5 days per week
  - Watches television or other indoor activities with the IC, at least 5 days per week
  - Other form of close contact with the IC deemed significant by the country network/country site study team

- **Concomitant Medications:** Country network/country site staff will ask participants to report non-study medication and concomitant medications/therapies taken during the study. Please see *CM - Concomitant Medications* CRF.
- **General Medical History and Physical Exam:** The following information will be captured on the *PE - Physical Exam and Medical History/Diagnoses* CRF.
  - Date of physical exam
  - Height: Height (or knee height, if participant is unable to stand) in accordance with the country network/country site’s standard operating procedure (SOP) to ensure that reported values have been measured in a standardized manner. See Attachment 4-4 for information on determining knee height. Height will be measured at the Baseline Visit for all participants. At subsequent visits, height (or length) is only measured for participants 21 years of age and younger.
  - Weight: Weight will be measured at every in-person visit by CRU site staff using the same scale at each study visit (if possible) in accordance with the country network/country site’s standard operating procedure (SOP) to ensure that reported values have been measured in a standardized manner. If there is more than one scale at the clinic, it is recommended that the site staff note which scale was used at each visit.
  - Diabetes status
  - HbA1C test results
  - COPD status
  - Other comorbidities
  - CBC results

  - BCG vaccination/scar
  - Pregnancy test results

- **TB Signs and Symptoms:** At the Screening Visit, country network/country site staff must ensure that potential Cohort B participants do not present with signs or symptoms of active TB. If signs or symptoms are present, a CXR or sputum culture or gene Xpert result must be obtained to rule out a diagnosis of active TB (see Common Protocol Section 4.2.1 #1 for TB signs and symptoms).
- **Mantoux Tuberculin Skin Test (TST):** Record the most recent TST results if done as part of standard of care, and a documented test result is available on *the TT - Tuberculin Skin Test (TST)* CRF.
- **Interferon-Gamma Release Assay (IGRA):** Whether done as part of standard of care or as part of the common protocol, record IGRA results on the *IG - Interferon Gamma Release Assay (IGRA)* CRF.
- **HIV History:** The *HI - HIV Status CRF* should be used to document whether an HIV test was conducted and whether the participant was previously diagnosed with HIV. Self-reported information is adequate, and it is not expected that they will provide supporting documentation of their diagnosis. If they have been diagnosed with HIV, ask their diagnosis date and whether or not they are currently on antiretroviral therapy (ART). If they are taking ART, ask them for the start date of their current prescribed regimen. If the exact dates of diagnosis and start date of their current ART regimen are unknown, ask participants to estimate the year. The *AT - Antiretroviral Therapy* CRF should be completed to capture this information.
- **Tobacco Smoking History:** See Section 4.1.2.2
- **Alcohol Consumption History:** See Section 4.1.2.2
- **Illicit Drug Usage History:** See Section 4.1.2.2
- **Follow-up Phone calls/Visits:** At follow-up visits, participants will be asked about TB Preventive Therapy and how long they have been taking prophylaxis since the recent exposure to a person with active pulmonary TB. This information should be documented on the *PH - TB Prophylaxis and TB Treatment History* CRF. For each follow-up phone call/visit, complete the *TS-Tuberculosis Symptoms* CRF to document whether the participant is experiencing signs/symptoms of TB. Ask participants whether they have been seen at a clinic since the previous visit and/or if any laboratory tests, CXRs, or other evaluations have been completed. If available, record the test results on the appropriate CRFs. If active TB is suspected at subsequent visits or between visits, and the visit is conducted via telephone, the participant will be asked to come to the clinic for a TB Activation Evaluation Visit. If the participant is already in the clinic for their follow-up visit, the TB Activation Evaluation Visit may be conducted on the same day.
- **TB Activation Visit:** The TB Activation Visit should be scheduled as soon as possible once the participant is suspected of having active TB. The full list of procedures to be conducted during the TB Activation Visit is provided in the Common Protocol Section 5.3.4, noting country standards of care. All corresponding CRFs should be completed to document the visit.

  If a Cohort B participant develops active pulmonary TB and is enrolled in Cohort A, the Cohort B TB Activation Visit and the Cohort A Baseline Visit may occur on the same day. However, if blood volume limits are exceeded by combining the visits, country networks/country sites are encouraged to conduct the visits on separate days in order that a full set of specimens can be collected for each visit, if time allows. If it is not possible to collect a full set of specimens for each visit, the specimen requirements in Cohort B take precedence over Cohort A specimens because TB activation is an important outcome of interest.

4.1.3.3. Clinical Evaluations for Cohort B

- Chest X-ray (CXR): CXRs will be conducted per protocol requirements. The results should be documented on the *CX - Chest X-Ray* CRF. If CXRs are completed as part of the standard of care within the protocol-specified timeframe, the CXR does not need to be repeated for the Common Protocol. Pregnant women are not required to have a CXR for the Common Protocol; however, if completed as part of standard of care, the results will be recorded on the *CX-Chest X-Ray* CRF.

  All CXR images will be labeled with:

  - PID
  - Study visit type (e.g., Baseline, Month 2, End of TX, TB Activation Evaluation)
  - Date of the CXR

  All personal identifying information must be removed from the CXR image, including name, address, DOB, and any identifier other than the Common Protocol PID that could link the image to the participant.

4.1.3.4. Clinical Laboratory Evaluations for Cohort B

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).

At the Baseline Visit, blood will be collected for HbA1C testing. Sputum (spontaneous) will be collected for GeneXpert and culture only if available.

If participants develop active TB or are suspected to have developed active TB, samples for clinical laboratory evaluations (e.g., CBC and lymphocyte count, HbA1c, HIV, CD4+ cell count, and sputum for AFB smear, culture, Gene Xpert, and DST) will be collected at the TB Activation Evaluation Visit, as required by the Common Protocol section 5.3.4. Refer to institutional SOPs and the *"RePORT Key Guidelines for the TB Laboratory"* and *"RePORT Key Guidelines for the Immunology Laboratory"* for specimen collection procedures. These key guidelines can be found in the Common Protocol Toolkit. Please document all tests in the appropriate CRFs as per the RePORT International Common Protocol Form Event Grid Cohort B Appendix 5-3 B.

Should participants have abnormal findings, country network/country site staff members are encouraged to provide the participant with the laboratory and/or clinical reports so the participant can follow up with their health care provider.

4.1.3.5. Research Laboratory Evaluations/Biorepository Storage for Cohort B

Blood specimens (whole blood for PAXgene RNA, plasma, and genetic analyses) will be collected at the Baseline and TB Activation Evaluation Visits for storage at the Biorepository. If blood collection volume in combination with other clinical or protocol blood collection requirements exceeds the allowable volume by the local IRB/IEC guidelines, or country-specific or other guidelines, as applicable, specimens will be prioritized as outlined in the "RePORT Key Guidelines for the Immunology Laboratory". Please document specimen storage in the *SS - Specimen Storage* CRF as per the RePORT International Common Protocol Form Event Grid Cohort B Appendix 5- 3B.

At the Baseline and TB Activation Visits, sputum will be collected for storage and for MTB isolate storage only if the participant is able to produce sputum.

It is important that country network/country site staff members are informed of specimen collection, temporary storage, and transportation requirements to ensure that the specimens are viable for long-term storage and future use. Refer to the country-specific laboratory manual for detailed instructions on specimen management.

4.1.3.6. Modified MRC Dyspnea Scale

Participants will be asked to complete the Modified MRC Dyspnea Scale at the Baseline Visit as well as at the TB Activation Visit. Please document the participant's response in the *MD - Modified MRC Dyspnea Scale* CRF.

4.1.4. Outcome Measures

In addition to the demographic, clinical, and laboratory data, several key outcome measures will be assigned to participants. The protocol provides a range of defined outcomes in Sections 4.4 (Cohort A) and 5.4 (Cohort B), which, together with the demographic, clinical, and laboratory data, will be used to characterize the population represented in the Biorepository specimens. When assigning the outcome measures, it is very important that the criteria in the protocol are strictly met. Supporting evidence must be recorded in the source documents.

NOTE: 'Treatment Outcome' and 'Completion of Therapy Status' outcome measures will not be assigned to Cohort A participants in the situations described below. However, these participants will be assigned a 'Study Outcome' of either "Mandatory withdrawal" or "Other", depending on the situation.

Cohort A Participants who:

- Do not meet confirmatory eligibility criteria (See protocol section 4.2.3)
- Are not HIV tested within 7 weeks of enrollment
- Do not have the minimum required baseline laboratory specimens collected within one week of starting anti-TB therapy
- Are inadvertently enrolled for any reason

Cohort B Participants who are inadvertently enrolled for any reason will be assigned an 'Other Outcome Status' of "Withdrawal".

4.1.4.1. Outcome Measures for Cohort A

All participants, except for those without culture-confirmed TB as described in protocol 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 Common Protocol section 4.3).

A. Treatment Outcomes for Participants Who Initially Have Bacteriologically Confirmed Drug-Susceptible TB

Participants who were initially confirmed to have active, DS TB will be evaluated for one of the following outcome status categories (refer to protocol Section 4.4 for definitions). World Health Organization (WHO) definitions were used with modifications. (See protocol section 4.4).

- Cured
- Treatment completed
- Treatment failed
- Died
- Lost to follow-up
- Not evaluated
- Treatment success

NOTE: The sum of "cured" and "treatment completed" will be combined to determine who meets the definition of treatment success. The WHO treatment outcome "Sustained treatment success" will not be assigned.

B. Clinical Outcomes

Some participants with bacteriologically confirmed TB at baseline 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.

C. Completion of Therapy Status

In addition to assigning a treatment outcome (Common Protocol section 4.4-1), all participants will be assigned a “Completion of Therapy Status” (Completion of adequate therapy or Incomplete), with the exception of those without culture-confirmed TB as described in Common Protocol Section 4.2.3. This information will be documented on the *ET - End of Treatment* CRF.

D. Additional Classifications

These classifications may also be assigned under specific circumstances. If a patient meets the criteria for bacteriological relapse, it is important that this be documented on the *ES - End of Study* CRF.

a. **Bacteriologic relapse*:** Participant met criteria for “Cured” or “Treatment complete” at the end of their 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.

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).

4.1.4.2. Outcome Measures for Cohort B

Active TB is the outcome measure of interest in this cohort. All participants must be assigned only one outcome, as defined in the Common Protocol Section 5.4. Please complete the “Outcomes” CRF to record the assigned outcome.

4.1.5. Visit Schedule Timeframes

Study visits must be conducted within the timeframes defined by the protocol. Due to factors such as holidays or inclement weather, it may be difficult to schedule or keep appointments precisely to the date. In order to allow for some flexibility, the protocol defines acceptable windows of time for each visit. Study visits are expected to be completed in one day, however, if for some reason this is not possible, participants may return on another day within the defined study visit windows.

It is strongly recommended that country networks/country sites develop a plan to ensure that the participants and/or parents/legal guardians are informed of the visit schedule. The country network/country site staff members are encouraged to schedule all follow-up visits while participants are in the clinic for Screening or Baseline Visits.

See Attachments 4-5A and 4-5B for sample calendars that may be used to determine Cohort A and Cohort B participant visit schedules, respectively. Each country network/country site will have a different population of participants with different needs and circumstances; therefore, the strategies to ensure that they return for follow-up visits will vary. Successful strategies may include but are not limited to: written reminder cards with study visit dates provided at each study visit; written reminders sent by mail; telephone calls; and home visits. In some cases, pre-arranged transportation is effective. Participants must also be instructed to contact country network/country site staff in case they develop signs/symptoms of treatment failure or TB relapse in Cohort A or develop signs of active TB in Cohort B.

4.1.5.1. Follow-up Visit Schedule for Cohort A

- **Month 2/8 weeks Visit (−2 weeks/+2 weeks):** The Month 2 Visit should occur 2 months/8 weeks after the Baseline Visit, but may occur as early as 6 weeks (42 days) and up to 10 weeks (70 days) after the Baseline Visit.
- **Month 6/26 weeks Visit (−4 weeks/+6 weeks):** The Month 6 Visit should occur 6 months/26 weeks following the Baseline Visit but may occur as early as 22 weeks (154 days) and up to 32 weeks (224 days) after the Baseline Visit.
- **End of Treatment Visit:** The End of Treatment Visit occurs after the final prescribed dose of TB treatment is taken. However, for many participants, the treatment regimen will be completed about 6 months after the Baseline Visit. Please note that an End of Treatment visit will not be scheduled if the participant’s treatment regimen is completed during the Month 6 visit window (22 weeks to 32 weeks). If the end of treatment regimen falls outside of the window (less than 22 weeks or more than 32 weeks after the Baseline Visit), the country network/country site staff will schedule an End of Treatment Visit. Please complete the *ET - End of Treatment* CRF.
- **Month 12/52 Week Visit (−4 weeks/+6 weeks):** The Month 12 Visit should occur 12 months/52 weeks after the Baseline Visit but may occur as early as 11 months/48 weeks months and up to 13.5 months (58 weeks) after the Baseline Visit. The visit may be conducted in person or by phone. Please complete the *ES - End of Study* CRF after this visit.
- **Treatment Failure/Relapse/Withdrawal Visit (TX F/R/W):** Participants who are suspected to have or experienced treatment failure or TB relapse; meet any other criteria for premature discontinuation (see protocol Section 6); or are withdrawn from the study for any reason, should have a final study visit at the time they are prematurely discontinued from the study. Treatment failure or TB relapse can be verified by documentation from the TX F/R/W Visit or a standard of care visit (tests performed by clinics or laboratories external to the country network/country site). When treatment failure or TB relapse is suspected or has already been confirmed from standard of care documentation, schedule the TX F/R/W Visit as soon as possible to ensure that biospecimen collection for the biorepository can be obtained as close to the occurrence of the defining event. This information should be captured on the *ES - End of Study* CRF.

4.1.5.2. Cohort B Visit Schedule

Screening, Baseline, and TB Activation Visits must occur in person. Follow-up visits in Cohort B may be conducted by phone or in-person.

- **Month 6/26 Week Visit (−4 weeks/+6 weeks):** The Month 6 Visit should occur 6 months/26 weeks following the Baseline Visit but may occur as early as 22 weeks (154 days) and up to 32 weeks (224 days) after the Baseline Visit.
- **Month 12/52 Week Visit (−4 weeks/+6 weeks):** The Month 12 Visit should occur 12 months/52 weeks after the Baseline Visit but may occur as early as 11 months/48 weeks months and up to 13.5 months (58 weeks) after the Baseline Visit.

- **TB Activation Evaluation Visit:** Participants who are suspected of having active TB or confirmed to have active TB should have a TB Activation Evaluation Visit as soon as possible so that specimens and information can be collected promptly. Participants should be instructed to contact study staff if they develop signs or symptoms of active TB or have been confirmed by an outside provider to have developed active TB. Participants will be discontinued from the study and informed that they may participate in the study as Cohort A participants if all eligibility criteria are met.

4.1.5.3. Missed Visits

The primary purpose of the Common Protocol is to establish a biorepository that is accompanied by a database of well-characterized specimens and standardized data for future TB research. It is, therefore, very important that country network/country site staff ensure that participants attend study visits within the protocol-defined windows and that all study visit requirements are conducted.

This section describes what should be done if participants do not complete their study visits within the allotted time windows. Missed visits should be documented on the *ES - End of Study* CRF for Cohort A participants. Whenever possible, the reason for a missed visit should be recorded, as well as the country network/country site's attempt to contact the participant.

A. Missed Visits in Cohort A

All visits must be completed within the allotted time window; otherwise, the visit will be considered a missed visit.

B. Missed Visits in Cohort B

Ideally, all Cohort B study visits/phone calls will be completed within the visit windows; however, if this is not possible, make every effort to complete the visit/phone call as soon as possible. If the participant does not return or cannot be reached by phone before the next study visit window opens, the visit will be considered a missed visit. For example, if the country network/country site staff is unable to reach a participant for the Month 6 Visit by 11 months after the Baseline Visit, then the Month 6 Visit will be considered a missed visit, because the Month 12 Visit window opens 11 months after the Baseline Visit.

4.1.6. Off Study Criteria for Cohorts A and B

The off-study criteria are listed in the Common Protocol Section 6 for both Cohort A and Cohort B. It is important that country network/country site staff document the reason that the participant is no longer participating in the study. For Cohort A, the *ES - End of Study* CRF should be completed. For Cohort B, the *OU - Outcomes* CRF should be completed.

4.1.7. Protocol Deviations

According to the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, Investigators are to implement the protocol in accordance with the protocol agreed to by funding organizations and which was given approval by the local IRB/IEC. Investigators should not implement any deviations from the protocol without agreement by the funding organizations and prior review and documented approval from the IRB/IEC of an amendment, except when necessary to eliminate an immediate threat to the participant, or when the changes involve only logistical or administrative aspects of the trial. If a deviation is implemented, the Investigator or designee should document and explain the deviation and report it to the IRB/IEC per institutional requirements and other regulatory authorities, as required.

4.1.8. Communications

Timely and accurate responses to country network/country site staff questions are essential to the success of the Common Protocol. It is recognized that situations arise that cannot be adequately addressed by referring to the protocol, MOP, *RePORT Key Guidelines for the TB Laboratory, RePORT Key Guidelines for the Immunology Laboratory*, or the *Common Protocol CRF Completion Instructions*. The country network/country site staff should email the support team designated by the country network for all questions to which they cannot find an answer. The RePORT Support Team will direct the questions to the appropriate person to respond to the country network/country site’s questions.

Attachment 4-1

RePORT International Common Protocol Study Screening and Enrollment Log

INSTRUCTIONS: Use this Screening Log to record all individuals approached to consider consenting for RePORT International Common Protocol participation, whether consent was given. Initial and date each entry. Enter new data since the Screening Log was previously transmitted to the Data Management Center by the first Friday of each month for those not enrolled only. **When the study accrual ends, delete the names/initials and dates of birth belonging to individuals who did not give consent.** Store the Screening Log in a double-locked area accessible to study staff only.

[1]**AGE** *(Record age in years (yr) or months (mo) if <1 yr of age at the time the individual was first considered for participation in the study, i.e., when approached to consent. If age is unknown, record 'UNK.' If age is not reported or not asked, record 'NR.')*			
[2]**BIRTH SEX** ***(Record only one)***			
1=Male	2=Female	UNK=Unknown	NR=Not reported or not asked
[3]**Race**			
[Enter country-specific race categories]			
[4]**Ethnicity**			
[Enter country-specific ethnicity categories]			
[5]**REASONS NOT CONSENTED** ***(Record all that apply)***			
1=Not interested in the study 2=Too time consuming/demanding 3=Afraid of loss of confidentiality	4=No direct benefit from participating 9=Does not want to report reason	10=Information not available to clinic or not asked 99=Other, specify	
[6]**REASONS INELIGIBLE** ***(Record all that apply)***			
1=No signs/symptoms of pulmonary TB (Cohort A) 2=Did not have a CXR consistent with TB, AFB + smear or GeneXpert + result (Cohort A) 3=Not willing to be tested for HIV (Cohort A) 4=Does not have a positive culture for Mtb 5=Has not had significant recent exposure to an adult with untreated or inadequately treated TB (Cohort B) 6=No evidence of LTBI by reactive IGRA or TST (Cohort B) 7=Suspected to have TB (Cohort B) 8=Does not agree to collection or storage of samples 9=Is not enrolled in the Parent Protocol (if appropriate) 10=Suspected/diagnosed MDR or XDR TB 11=Extrapulmonary TB only 20=Received more than 1 week of anti-TB treatment (Cohort A)	22=Plans to move away from area 23=Active psychiatric condition that interferes with ability to give informed consent or adhere to study requirements 24=Alcohol dependence that interferes with ability to give informed consent or adhere to study requirements 25=Drug dependence that interferes with ability to give informed consent or adhere to study requirements 26=Currently imprisoned 99=Other, specify		
[7]**REASONS NOT ENROLLED WHEN ELIGIBLE** ***(Record all that apply)***			
81=Unable to locate or contact	82=Withdrew consent	83=Unwilling to comply with all study requirements	99=Other, specify

RePORT International Common Protocol Study Screening and Enrollment Log

#	*DO NOT ENTER IN DB* INITIALS OF INDIVIDUAL	AGE YR OR MO (IF <1 YR)[1]	BIRTH SEX[2]	RACE[3]	ETHNICITY[4]	IF APPROACHED BUT NOT CONSENTED, PROVIDE REASON(S)[5] STOP *RECORD 'NA' IF CONSENTED*	DATE CONSENTED (dd-mm-yyyy)	DATE SCREENED (dd-mm-yyyy)	DATE ENROLLED (dd-mm-yyyy) RECORD 'NA' IF NOT ENROLLED	PID	REASON(S) INELIGIBLE[6] STOP *RECORD 'NA' IF ELIGIBLE*	REASON(S) NOT ENROLLED WHEN ELIGIBLE[7] *RECORD 'NA' IF ENROLLED*	*DO NOT ENTER IN DB*	
													STAFF INITIALS AND DATE	DATE DATA TRANSMITTED
1		___ ☐ Yr ☐ Mo												
2		___ ☐ Yr ☐ Mo												
3		___ ☐ Yr ☐ Mo												
4		___ ☐ Yr ☐ Mo												
5		___ ☐ Yr ☐ Mo												

Attachment 4-2

Sample Contact Information Form

INSTRUCTIONS: This form should be completed by a country network/country site staff member with the help of the participant. This form is to be filed separately from study data and under double locks.

Tell the participant:

The information you provide will help us get in touch with you later. This information is only to help us find you so that we can schedule a study appointment, remind you about your study appointment, or check to see how you are doing. We will keep this form under double locks and separate from any other research records so that your contact information stays private.

1. Name: ____
2. Address:
____
____
____

3. Email address:______________________________

4. Home Telephone Number:____________________

4a. Can we leave a message?
☐ Yes
☐ No ***(Go to Q5)***

4b. ***If yes:*** Is it ok to say who we are or where we are calling from?
☐ Yes ***(Go to Q5)***
☐ No

4c. ***If no:*** What should we say? ________________________________

5. Mobile Phone Number: __

5a. Can we leave a voice mail message? ☐ Yes ☐ No

5b. Can we send you a text message? ☐ Yes ☐ No

If yes to Q5a or Q5b:

5c. If it is ok to leave a voice mail message, or ☐ Yes ***(Go to Q6)*** send a text message, is it ok to say who we are ☐ No

or where we are calling from?

5d. ***If no:*** What should we say? ____

If yes to Q4a or Q5a:

6. When would be the best time(s) to call you? _____

Is it ok to send you a letter if we cannot reach you ☐ Yes

by phone or email? ☐ No

7. If we cannot reach you by phone, email, or letter, can we ☐ Yes

a- contact a family member or friend who might be able to ☐ No ***(Stop)***

b- help us reach you?

If yes to Q8, provide contact information for the family member or friend:

8. Name: ____

9. Address:

____

____

____

10. Email address: __

11. Home Telephone Number: ______

12a. Can we leave a message? ☐ Yes***(Go to Q13)***

☐ No

12b. ***If yes:*** Is it ok to say who we are or where we are calling from? ☐ Yes ***(Go to Q13)***

☐ No

12c. ***If no:*** What should we say? ____

12. Cell Phone Number: ____

13a. Can we leave a voice mail message? ☐ Yes

☐ No

13b. Can we send a text message? ☐ Yes

☐ No

If yes to Q13a or Q13b:

13c. If it is ok to leave a voice mail message or ☐ Yes
send a text message, is it ok to say who we are ☐ No
or where we are calling from?

13d. ***If no:*** What should we say? ____

Study Coordinator/Designee:

______________________ ________________________ ____________
Signature Print Name Date

Attachment 4-3 A

RePORT International Common Protocol Form Event Grid – Cohort A

Each visit indicates the complete set of potential CRFs that may be required as per the Common Protocol. Please refer to the Common Protocol document, section 4. Cohort A: Participants with Active Pulmonary TB for complete details on all visits. Information on the CRFs can be found in the Common Protocol Toolkit.

Form Name	**Screening**	**Baseline**	**Month 2**	**Month 6**	**End of Treatment**	**Month 12**	**Treatment Failure** **Relapse** **Withdrawal**
IA – Inclusion and Exclusion Criteria	X						
VT – Visit Tracking		X	X	X	X	X	X
HT – Household Tracking[a]		X					
CM - Concomitant Medications		X	X	X	X	X	X
PH - TB Prophylaxis and TB Treatment History		X	X	X	X	X	X
AT - Antiretroviral (ARV) Therapy		X	X	X	X	X	X
DM – Demographics[b]		X					
PE – Physical Exam and Medical History		X	X	X	X	X	X
SU – Substance Usage		X	X	X	X	X	X
HI - HIV Status		X	X	X	X	X	X
PO – Pregnancy/Birth Outcome			X	X	X	X	X
TH – Tuberculosis Treatment History		X					
TS - Tuberculosis (TB) Symptoms		X	X	X	X	X	X
SS – Specimen Storage		X	X	X	X		X
MD- Modified MRC Dyspnea Scale		X			X		X
CX - Chest X-Ray		X	X	X	X		X
IG – Interferon Gamma Release Assay							X
AF - Acid-Fast Bacilli (AFB)		X	X	X	X		X
MT – *M. tuberculosis* Culture Results		X	X	X	X		X
GX - GeneXpert MTB-RIF Ultra		X					X
DS - Drug Susceptibility Testing (DST) Results		X					X
ET – End of Treatment					X		X
ES – End of Study						X	X

a – Use the Cohort A specific version of the HT form

b– Use the Cohort A specific version of the DM form

Attachment 4-3 B

RePORT International Common Protocol Form Event Grid – Cohort B

Each visit indicates the complete set of potential CRFs that may be required as per the Common Protocol. Please refer to the Common Protocol document Section 5. Cohort B: Household Contacts (HHCs) or Close Contacts of Active TB Patients for complete details on all visits.

Form Name	**Screening**	**Baseline**	**TB Activation**	**Month 6**	**Month 12**	**Premature Discontinuation**
IB – Inclusion and Exclusion Criteria	X					
VT – Visit Tracking		X	X	X	X	X
HT – Household Tracking[a]		X				
CM - Concomitant Medications		X	X	X	X	X
PH - TB Prophylaxis and TB Treatment History		X	X	X	X	X
AT - Antiretroviral (ARV) Therapy		X	X	X	X	X
DM – Demographics[b]		X				
PE – Physical Exam and Medical History		X	X	X	X	
SU – Substance Usage		X	X	X	X	X
HI - HIV Status		X	X	X	X	X
PO – Pregnancy/Birth Outcome			X	X	X	X
TS - Tuberculosis (TB) Symptoms		X	X	X	X	X
SS – Specimen Storage		X	X			
MD- Modified MRC Dyspnea Scale		X	X			
CX - Chest X-Ray		X	X	X	X	X
TT – Tuberculin Skin Test (TST)		X	X			
IG - Interferon Gamma Release Assay		X	X			
AF - Acid-Fast Bacilli (AFB)		X	X			
MT – *M.tuberculosis* Culture Results		X	X			
GX - GeneXpert MTB-RIF Ultra		X	X			
DS - Drug Susceptibility Testing (DST) Results		X	X			
OU – Outcomes			X		X	X

a– Use the Cohort B specific version of the HT form

b– Use the Cohort B specific version of the DM form

Attachment 4-4

Measuring Knee Height

Adapted from Jawaharlal Institute of Postgraduate Medical Education & Research's Anthropometric Measurements Standard Operating Procedures Version 1.0 (23 May 2014)

Knee height is only measured in participants who are unable to stand for a standing height measurement. For country networks/country sites that do not have an SOP to measure knee height, these instructions may be used.

Shoes and very heavy socks should be removed. It is necessary to perform the knee height measurement on the bare knee.

Measure the right leg unless the left leg is obviously longer than the right leg or if the right leg cannot be measured for some other reason (e.g., cast, amputation, sores, etc.).

If the participant can sit (Exhibit 1A): Tape the zero end of the nylon or plastic measuring tape to the base of the wall, where it meets the floor. Ask the participant to sit in a chair next to the wall with their foot against it and bend their knee at a 90º angle. Position the foot on the floor so the ankle is at a 90º angle. Record the distance between the floor/foot and the suprapatella (top of the knee, just proximal to the kneecap).

If the participant cannot sit (Exhibit 1B): The participant may lie supine while the examiner places their right knee and ankle at 90º angles. In this position, the measured distance is between the landing point and the suprapatella point from the lateral side.

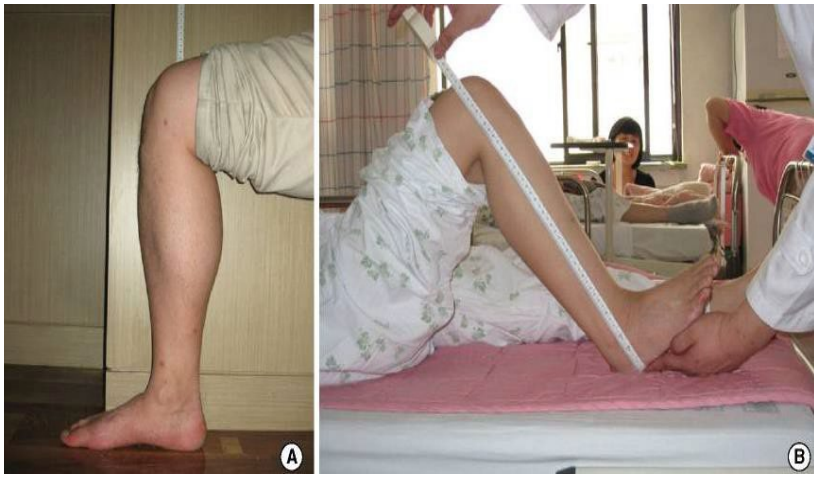

Exhibit 1. Participant position for knee height

Attachment 4-5 A

RePORT International Common Protocol Sample Cohort A Study Visit Calendar

Instructions:

1. Enter PID number, date of Baseline Visit, and duration of anti-TB treatment
2. Schedule next visit(s) within visit window dates
3. Enter scheduled visit dates and file in the participant's record
4. Modify the schedule based on actual visit dates, as needed
5. Provide the participant with their study visit schedule, according to the country network/country site's standard.

PID: ____________________________

Date of Baseline Visit: ____________________________

Start Date of TB Treatment: ____________________________

Anticipated End Date of TB Treatment: ____________________________

Visit	Expected Visit Date	Beginning of Visit Window	End of Visit Window	Scheduled Visit Date	Actual Visit Date
Baseline					
Month 2					
Month 6					
End of TX[1]					
Month 12 (phone call or visit)					

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[1] The End of Treatment Visit will not need to be scheduled if the end of the TB treatment regimen falls within the Month 6 Visit window.

Attachment 4-5 B

RePORT International Common Protocol Sample Cohort B Study Visit Calendar

Instructions:

1. Enter PID number and date of Baseline Visit
2. Schedule next visit(s) within visit window dates
3. Enter scheduled visit dates and file in the participant's record
4. Modify schedule based on actual visit dates, as needed
5. Provide the participant with their study visit schedule, per the country network/country site's standard

PID: ___________________________

Date of Baseline Visit: ___________________________

Visit	Expected Visit Date	Beginning of Visit Window	End of Visit Window	Scheduled Visit Date	Actual Visit Date

5. TRAINING

5. TRAINING

This chapter describes the country network/country site staff training requirements that must be completed prior to implementing the Common Protocol. The country network/country site Principal Investigators (PIs) are responsible for ensuring that staff members are appropriately trained and qualified to perform their jobs. This chapter provides guidance on recommended training courses that should be completed before implementing the Common Protocol. The training listed in this chapter is not meant to be an exhaustive list. Recommended trainings are described in Tables 5.1 – 5.4.

Table 5.1 Recommended and Required Training: General

Training Topic	Who Should Be Trained?
Human Subjects Protection (HSP)	All staff involved in the study
Good Clinical Practice (GCP)	All staff involved in the study
Good Clinical Laboratory Practice (GCLP)	All laboratory staff

Table 5.2 Recommended and Required Training: Protocol-Specific

Training Topic	Who Should Be Trained?
Common Protocol and MOP Training	All staff involved in the study
Common Protocol – Read the Materials	All staff involved in the study
MOP – Read the Materials	All staff involved in the study
Case Report Form (CRF) Completion Training	All applicable staff who complete CRFs, enter data, or manage the process
Common Protocol CRF Completion Instructions and CRFs – Read the Materials	All applicable staff who complete CRFs, enter data, or manage the process
The country network/country sites' Clinical Quality Management Plans (CQMPs)	Study Coordinators, quality assurance, and data management, and other applicable staff
Relevant institutional and study-specific standard operating procedures (SOPs) and work instructions	Various study staff, as applicable

Table 5.3 Recommended and Required Training: Data Management

Training Topic	Who Should Be Trained?
Data entry processes (data entry, updates, discrepancy resolution)	All staff who enter or manage the entry of the Common Protocol data
Data Management SOPs	Various study staff, as applicable
Data Quality Management Plan	Various study staff, as applicable

Training Topic	Who Should Be Trained?
Data Transfer	Applicable data management and other staff
FreezerPro® (or equivalent system)	Country network/country site data management and laboratory staff who enter or manage specimen data entry in FreezerPro® or are otherwise involved with specimen processing, shipping, and tracking

Table 5.4 Recommended and Required Training: Laboratory

Training Topic	Who Should Be Trained?
Laboratory Manual Training	All laboratory staff
RePORT International Laboratory Manual – Read the Materials	All laboratory staff
Relevant Laboratory and Study-Specific Procedures	Relevant Laboratory and Study-Specific Procedures
International Air Transport Association (IATA) Certification Training to ship dangerous goods	At least one staff member who will perform the task (back-up is recommended)

5.1. Documentation of Site Staff Training

Staff training should be documented with a certificate or within a training form. Training documentation should consist of the trainee's name; the date, title, and main content of the training; and the trainer's name and affiliation (if applicable). A sample template for documenting staff training is available in this section of the MOP (Attachment 5-1). Signed training attendance rosters from each event should also be maintained as supporting evidence.

5.1.1. General Staff Training – Human Subjects Protection Training, and Good Clinical Practice Training

All country networks/country sites participating in the Common Protocol must comply with host country and US regulations for research involving human participants and be in accordance with the International Conference on Harmonisation (ICH)/GCP guidelines. See Section 2 of this MOP for additional information on considerations for human participants.

HSP and GCP training are required for all country network/country site staff and are prerequisites for participation in the Common Protocol. Periodic recertification may be required according to your institution's policy. Study staff members who are required to complete HSP and GCP training include those individuals engaged in the conduct of research who:

- Interact with living individuals by performing invasive or noninvasive procedures for research purposes (e.g., obtaining consent, performing study visits, drawing blood, collecting other biological samples, dispensing drugs, administering other treatments, employing medical technologies, utilizing physical sensors, utilizing other measurement procedures); or
- "Obtain individually identifiable private information" that is considered to be "engaged" in research.

Examples of study staff who require training:

- Physicians/clinicians/nurses on staff as full-time, part-time, or on fellowship who interact with study participants or their individually identifiable private information for research purposes.
- Pharmacists, pharmacy technicians, data managers, laboratory staff, and counselors. The level of training may also be at the discretion of the investigator, depending on the individual's level of involvement in the research.

All other staff who are in supporting roles, such as couriers, drivers, receptionists, and administrative staff, should receive training on the protection of participant privacy and confidentiality.

5.1.2. Good Clinical Laboratory Practice Training

GCLP will be followed as part of the Common Protocol. GCLP embraces both the research/preclinical and clinical aspects of Good Laboratory Practice (GLP). Complying with GCLP is an ongoing process that is central to optimal clinical research laboratory operations. GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results that support clinical research studies will be produced in an environment conducive to study reconstruction.

More specific information about GCLP standards can be found in the document *DAIDS Guidelines for Good Clinical Laboratory Practice Standards*.

5.2. Protocol-Specific Training

All country network/country site staff members who implement the Common Protocol should be appropriately trained on the Common Protocol, the accompanying MOP, CRFs, and all relevant procedures that affect protocol implementation. It is the responsibility of the country network/country site PI to ensure that all staff are appropriately trained and qualified to perform their tasks before they begin work.

5.2.1. Common Protocol and Manual of Operating Procedures Training

All staff members who implement the Common Protocol are required to be trained on the protocol and MOP. It is expected that each country network/country site's management staff will be adequately trained and familiar with the Common Protocol and MOP to have the ability to train other country network/country site staff on the documents. It is required that all Common Protocol staff members certify that they have read the Common Protocol and MOP, understand the contents presented in the materials, and complete basic in-person and/or Web-based training that highlights the major points of each document.

5.2.2. Case Report Form Completion Training

All study staff who complete CRFs, enter data, or manage the process are required to be trained on CRF completion. The minimum requirements include a staff member review of the CRFs and the CRF Completion Instructions document. Staff should also acknowledge that they understand the contents presented in the material. It is highly recommended that each country network/country site provides a general CRF completion training session for all staff who qualify as part of the Common Protocol training to train site managers in the CRF completion nuances and procedures, and to better prepare them to train staff at their sites. Country networks/country sites must ensure that all appropriate staff members have been trained to complete the CRFs before they begin work on the Common Protocol.

5.2.3. Country Network/Country Site Clinical Quality Management Plan Training

It is highly recommended that each country network/country site establish and implement a CQMP (see Section 3 for details). As part of this plan, and to support its implementation, all appropriate country network/country site staff should be trained on the CQMP. The specific details regarding how CQMP training will be conducted are at the discretion of each country network/country site PI.

5.2.4. Training for Relevant Standard Operating Procedures and Work Instructions

In order to effectively implement the Common Protocol, each country network/country site will need to have a series of standard operating procedures (SOPs) and work instructions in place that provide details about how various processes are conducted. To facilitate the correct implementation of these procedures, the PI is responsible for ensuring that all appropriate country network/country site staff have been trained on each SOP or work instruction. The specific details about how these trainings will be conducted are up to the discretion of each country network/country site PI.

5.3. Data Management Training

This section describes the types of data management training that should be conducted at the country networks/country sites. Individual data management training needs for each country network/country site will vary depending on the systems and processes that are in place. The PI and Data Manager are responsible for ensuring that the full training needs of their country network/country site have been met prior to the implementation of the Common Protocol and during updates and the addition of new staff, as needed.

5.3.1. Data Entry, Data Management Standard Operating Procedures, and Data Quality Management Plan Training

All staff who enter or manage the entry of Common Protocol data must be trained on the system used to collect data. Appropriate data management and other staff should also be trained in the country network/country site’s data management SOPs and data quality management plan.

5.3.2. Data Transfer Training

RICC will assist in training and supporting end users with REDCap system functionality and technical issues. The sites should maintain documentation illustrating the completion of training activities. All site staff must be able to show proof of training on REDCap prior to usage of the system. Biospecimen tracking and management for the Common Protocol will be performed using FreezerPro®. The system should be installed, and staff should be trained in its use, before country networks/country sites are approved for study activation. Country network/country site data management and laboratory staff who enter or manage the entry of specimen data or are otherwise involved with specimen processing, shipping, and tracking should be trained to use the FreezerPro® system.

5.4. Laboratory Training

This section describes the laboratory training that should be implemented at the country networks/country sites. Individual circumstances at each country network/country site may vary, and other types of training may be needed as well. The PI and Laboratory Manager are responsible for ensuring that the full training needs of their country network/country site have been met.

5.4.1. Laboratory Manual Training

All laboratory staff who work with Common Protocol specimens, and/or clinic staff collecting Common Protocol specimens, must be trained on the *RePORT International Laboratory Manual*. The minimum requirements include staff review and documentation of their acknowledgement of understanding of the contents of the manual. Each country network/country site should provide a general laboratory training session for all qualifying staff, including clinic staff responsible for specimen collection and transport. The country network/country site will provide laboratory training to staff as part of the Common Protocol training to train site managers in RePORT laboratory procedures and to better prepare them to train staff. Country network/country site PIs and Laboratory Managers should ensure that all laboratory and relevant clinic staff members are qualified and have been trained to complete procedures as specified in the *RePORT International Laboratory Manual*, before they begin work on the Common Protocol.

5.4.2. Training for Relevant Laboratory Procedures

All laboratory staff should be appropriately trained to perform their tasks. Appropriate laboratory and other staff should also be trained on the country network/country site's laboratory SOPs and laboratory quality management plan. Training should be provided by the country network/country site, and other resources should be brought in to assist with this process if the country network/country site lacks qualified in-house resources.

5.4.3. International Air Transport Association Certification Training

At least one individual from each country network/country site must hold a current certification for shipping dangerous goods, such as IATA or its equivalent. It is also recommended that backup staff are trained and certified to perform this function, if possible. The IATA certificate or its equivalent must be kept on file at the country networks/country sites and renewed every two years. Country networks/country sites are required to comply with local regulations that may necessitate additional permits/certificates for the transportation of hazardous goods (such as blood specimens). The country networks/country sites should be assessed annually to ensure that certification to ship dangerous goods is current and on file.

5.4.3.1. Training Frequency

- Once initial training has been completed, employees must receive regular training to remain updated on any changes to the regulations.
- Training is required every time changes in the regulations occur that pertain to the hazardous materials that the employee handles within their job function.
- Refresher or recurrent training for staff involved in the movement of dangerous goods by air must be received within 24 months of the previous dangerous goods training to make sure that the employee's knowledge is up to date.

5.4.3.2. Dangerous Goods Certification Training Resources

Certification and training courses in shipping dangerous goods are offered through the following (as well as other) sources. The sources listed are not specifically endorsed by this MOP, and country networks/country sites are responsible for selecting their own training sources. Below are links and contact information for training courses:

- Saf-T-Pak, Inc.
- Dangerous Goods International (DGI)

Attachment 5-1

RePORT International Common Protocol Sample Documentation of Training Form

This form should be used and modified to document that the training requirements outlined in Section 5 of the RePORT International Manual of Operating Procedures were completed.

Country Network/Country Site Name: ____________________________

Name of Staff: ____________________________

Date Started on Project: (DD/MON/YYYY) ____________________________

Position: ____________________________

Training (acknowledgement of participation in training and/or review and understanding of documents)	Check if N/A	Date Completed	Signature
Common Protocol – In-person training			
Common Protocol – Read protocol and acknowledged understanding of contents			
Case Report Form (CRF) Completion Instructions review and acknowledgement of contents			
Manual of Operating Procedures (MOP) review and acknowledgement of contents			
Chest X-Ray Reader Training			
Laboratory Procedures (specify)			
RePORT International Laboratory Manual			
FreezerPro®			
QuantiFERON®-TB Gold Plus (QFT-Plus)			
Clinical Quality Management Plan			
Site Standard Operating Procedures (SOPs) and other documents (specify)			
Other			

6. DATA MANAGEMENT OVERVIEW

6. DATA MANAGEMENT OVERVIEW

This section outlines the data management responsibilities for both local teams at the participating country networks/country sites in RePORT International and the central team at the Coordinating Center (RICC). These guidelines ensure compliance with the International Council for Harmonisation (ICH) Guidelines, Good Clinical Practices, 21 CFR Part 11, and relevant FDA regulations.

6.1. Data Collection

Data collection for RePORT should follow standardized templates and tools to ensure consistency across sites and adhere to project expectations. Using standardized tools and adhering to established templates ensures all required data items are collected, and data can be harmonized from across multiple collection sites. RePORT has established the following standardized tools and templates for use by the data collection sites.

REDCap is the primary data collection system used in RePORT International. A centrally developed REDCap build has been created by the RePORT International Coordinating Center (RICC) for the collection of clinical data. Sites can request access to the build and associated CRF packets from the RePORT Common Protocol International Tool Kit. Clinical data collection sites can install this REDCap build locally to ensure all data elements required by the RePORT International Common Protocol are collected at each participant visit for all cohorts. In the event that a site will collect data above and beyond the expectations of the Common Protocol, sites can modify the centrally developed REDCap build to add additional data items as needed. If changes are needed to the centrally developed REDCap build, it is critical that sites do not remove items or rename existing data items. If a change is required to add a new option to a standard drop down collection menu, this update must be discussed with RICC to ensure the option can be accounted for during future data harmonization.

Case Report Forms (CRFs) are study data collection instruments that have been centrally developed by RICC. When implemented in an electronic data capture software such as REDCap, they are also known as electronic case report forms (eCRFs). Clinical data collection sites can use these eCRFs to ensure all data elements required by the RePORT International Common Protocol are collected at each participant visit for all cohorts. The CRFs are designed to easily transcribe the information back to the centrally developed REDCap eCRF build. In the event a site will collect data above and beyond the expectations of the Common Protocol, sites can modify the centrally developed eCRFs to add additional data items as needed. If changes are needed to the centrally developed CRFs it is critical that sites do not remove items or rename existing data items. If a change is required to add a new option to a standard collection, this update must be discussed with RICC to ensure the option can be accounted for during future data harmonization.

FreezerPro® is the laboratory information system used in RePORT International for specimen tracking and management. RICC provides access to FreezerPro® for all sites to log information regarding the collection and storage of biological specimens collected for the RePORT International Common Protocol. Any site collecting and storing specimens for RePORT International can request access to FreezerPro® from RICC. Prospective collections can be logged to FreezerPro® to track collection and storage of new specimens. Information from existing specimens can also be migrated into FreezerPro® from legacy specimen databases. Sites who need assistance with FreezerPro® or assistance with migrations into FreezerPro® should visit the RePORT International Common Protocol Tool Kit, where they will find details on licensing, hardware peripherals, configuration and setup support, training options, and more.

6.2. Data Quality Assurance

Clinical site data quality assurance (QA) is a crucial part of the research process that ensures data are accurate, reliable, and compliant with regulations. Each site will be responsible for their own data quality assurance. Each site should create standard operating procedures (SOPs) as necessary to define their data quality assurance process. Data should be reviewed and confirmed within the original data source via a signature by the relevant site Investigator. This self-monitoring can ensure a well-run research study and identify and mitigate issues before they are identified by monitoring entities, avoiding the need for time-consuming fixes. Internal monitoring includes monitoring for proper informed consent documentation/records, eligibility criteria, and data quality.

Data quality assurance involves the organization and retention of key study documentation, known collectively as the Regulatory Binder. The Regulatory Binder is organized and retained to support monitoring and auditing by Sponsors and regulatory authorities. The Regulatory Binder is maintained by the site staff. See section 3.2.1 for more information.

Data quality assurance performed centrally will also be ensured by RICC, who expect to receive timely, high-quality data. RICC data management staff utilize features in REDCap to automate certain aspects of data quality and timeliness checks. Edit checks will be created within the electronic Case Reports Forms (eCRFs) to identify potential errors at the time of site data entry for key data elements by flagging required fields, as well as potential errors or questionable data. Queries will then be issued which will require timely responses from the sites.

Data completeness is monitored by various methods throughout the study build process. One method is through the use of skip logic on forms, directing sites to complete each required field based on previously answered questions and further preventing sites from completing unnecessary fields. If data are not compliant with the skip logic provided, automated queries appear for the sites at the time the form is saved. In addition, RICC staff will incorporate range checks in the study build by defining expected ranges for specific fields. An example of this is for laboratory values. If a site enters a value outside of the pre-defined range, an automated query will appear upon saving the eCRF, for which the site must either correct the data, or issue a response for the protocol data manager data to review.

6.3. Data Transfer Protocols

Data will be transferred from country data teams to RICC for QA and harmonization in order to satisfy cross-country concepts, to produce dashboards, to generate analysis data sets for publications, to provide enrollment and specimen availability summaries for sponsors, and more. It is critical these data transfers adhere to standards set forth by RICC to ensure all requirements for transfer agreements have been satisfied, data are sent following established transfer methods to ensure security, data are received timely, and all transferred files meet expectations for completeness, format, and layout.

6.3.1. Data Agreements

Any site needing to perform a data transfer must first establish a Data Use Agreement (DUA) or Data Transfer Agreement (DTA) to satisfy any local rules and regulations pertaining to the data collection site. RePORT International is a collaboration across multiple countries that each have a unique set of rules and regulations around data sharing. RICC can assist investigators to navigate these policies and procedures to ensure all necessary documentation is in place before data are shared.

6.3.2. Secure Data Transfers

Data transfers to RICC must use secure data transfer methods. A variety of tools are available, including commercial tools such as ownCloud (a Frontier Science supported commercial system) and Box (supported by Rutgers University) as well as Frontier Science's secure Data Submission System (DSS). Using these tools provides a number of additional benefits beyond data security. Transferring files using a secure tool also provides notification to the data receiver alerting them that a file is available, provides notification to the data sender that the file was received, and keeps an audit trail of file transfers.

6.3.3. Timeliness of Data Transfers

Some data transfers to RICC will satisfy a specific analysis need and will require a single, one-time transfer. RICC may also establish recurring data transfers in support of ongoing QA or reporting, annual meeting summaries, or refreshing of dashboards. All data transfer requests will include a deadline. Exceeding a deadline may require

RICC to exclude that country’s data from the analysis or report. If a data transfer will not meet the deadline, RICC must be notified as soon as possible to allow for planning and reconsidering timelines.

6.3.4. Data Completeness

All recurring data transfers are expected to be cumulative. This ensures all data updates to prior records and all newly transferred records are accounted for. If a recurring transfer is not cumulative, RICC must be notified, and a detailed list of data changes must accompany the data transfer.

6.3.5. Data Format and Layout

Data must be transferred to RICC using established templates whenever possible. If a template has not been established or will not be used for data transfer, all files must be accompanied by a codebook describing each data header and coded value. Using data collection tools such as the centrally developed REDCap and FreezerPro® and adhering to established transfer templates such as the data summary for the RADAR dashboard will ensure that data transfers follow the expected format and layout.

6.4. Data Receipt and Validation

6.4.1. Data Receipt Confirmation

All data transfers to RICC will notify the data sender if the files were successfully received or not. In the event files were not successfully received, the data sender and RICC may need to find an alternative data transfer method. A summary of records received will be sent to the data sender to ensure file completeness.

6.4.2. Data Receipt Validation

Once a file has been successfully received and confirmed, RICC will review the file for completeness, format, and layout. Issues identified by RICC, including unexpected column headers, unexpected or incorrect code sets, improperly coded or formatted data, or other suspected irregularities with the data structure will be confirmed with the data sender. Minor data issues may only require written explanation, for example, confirming what an unexpected code value represents. Other issues, such as missing data columns or improperly translated code sets, may require the data sender to reformat and resubmit to RICC. It is critical that the data sender review and reply to queries from RICC regarding validation of their data to ensure issues are resolved timely and do not prevent files from being harmonized and included in the larger data set.

6.5. Central Data Quality Assurance

All data will be reviewed by data managers at RICC for completeness and accuracy, and this work will be guided by a data management plan (DMP) based on data management best practices. This document will list primary milestones, data quality assurance and quality control activities, and primary roles and responsibilities, and will summarize any other controlled documents that will be followed by staff for completion of all data management workflows. This DMP will serve as a set of detailed instructions for data management staff performing quality assurance tasks. In addition, data review meetings will be conducted on a regular basis, whereby data management experts can discuss findings and corrective actions as well as data harmonization efforts.

6.6. Query Management

6.6.1. Query Generation

Errors identified by RICC will prompt data managers to issue queries for ensuring resolution of any possible issues. REDCap provides various tools for sites and data managers to monitor and manage data queries and nonconformant data, as well as view expected visits and overdue eCRFs. RICC also conducts manual review of certain data points and will issue queries if a review suggests that there may be discordant data.

6.6.2. Query Resolution

Queries should be resolved by the sites within four weeks of receipt. All query responses should be documented by the site. Upon receipt of the query response, RICC will communicate with a site if the query response is satisfactory or if additional clarification or information is needed. RICC data managers will also be responsible for rerunning data quality checks after query resolution to ensure data accuracy.

6.6.3. Query Tracking

RICC maintains a tracking system to monitor query status, response time, and completion. All updates to the RePORT International central database will be tracked via an audit trail, recording and date-stamping every suspected error in a database log. Error-monitoring software will be used to detect when data have been corrected or when a site's explanation that the data are correct is accepted and update the error-tracking log with the date of resolution.

6.7. Data Harmonization

Data harmonization is essential to ensure that data collected across different sites can be integrated, analyzed, and reported in a unified format. This process involves mapping data from local collection tools to the centrally defined data structures, ensuring consistency, completeness, and accuracy in cross-site comparisons and analyses. Harmonization efforts are critical for creating analysis datasets, generating cross-country reports, and supporting decision-making.

6.7.1. Harmonization Requirements

Data harmonization for RePORT International requires that all sites use standardized tools and templates, such as the centrally developed REDCap build and FreezerPro® systems, as well as predefined data collection instruments such as case report forms (CRFs) and data transfer templates. Any deviations or additions to these standard tools or instruments must be approved by the RePORT International Coordinating Center (RICC) to maintain data consistency. Additionally, all sites must ensure that data variables and coding structures align with the established data dictionaries and codebooks provided by RICC. This includes adherence to the Common Protocol and ensuring that any site-specific modifications do not conflict with the harmonization framework.

6.7.2. Data Mapping

Data mapping is the process of linking data fields from local databases to the centrally defined data models. This ensures that data from different sources can be combined and analyzed without discrepancies. RICC provides guidance and support to sites for the mapping process, including:

Data Dictionary Alignment: Sites must ensure that their data dictionaries match the central dictionary developed from the common protocol. This involves using the same field names, formats, and coding standards.

Variable Harmonization: When collecting additional data, sites should use existing field structures whenever possible. If new variables are necessary, they must be mapped appropriately to ensure compatibility with central data structures.

Controlled Vocabulary: Use of controlled vocabularies for fields such as diagnoses, medications, and procedures ensures that data across sites are comparable and consistent.

6.7.3. Harmonization Checks

The harmonization process includes several validation steps to ensure data integrity:

Consistency Checks: Data from each site will be reviewed for consistency with the centrally defined protocol. This includes reviewing data for missing or out-of-range values and checking for discrepancies between datasets.

Cross-site Comparisons: Data will be compared across sites to identify any variations that could impact the overall study results. Differences in data collection methodologies or variable definitions will be addressed to ensure compatibility.

Automated Harmonization Tools: RICC employs automated tools to check for harmonization issues, such as incompatible data formats or missing fields. These tools generate reports that highlight areas requiring attention before data can be integrated into the central database.

6.7.4. Reporting and Documentation

Each site must document its data harmonization efforts, including details on any deviations from the standardized templates, mappings performed, and resolutions to identify issues. This documentation is crucial for transparency and for ensuring that the harmonization process is traceable and auditable. Regular data review meetings will be conducted with site data managers and RICC to discuss any harmonization challenges and to ensure that data alignment is achieved across all participating sites.

6.8. Query Documentation and Recordkeeping

Each site should establish procedures for maintaining the Regulatory Binder and source data maintenance, as well as procedures for data quality assurance. All records must be retained at a minimum for the duration of the RePORT International project. RICC will store all of its project standard operating procedures and other related project documentation in an essential document library.

6.9. Staff Training

RICC will assist in training and support end users with REDCap system functionality and technical issues. The sites should maintain documentation demonstrating completion of training activities. All site staff must be able to show proof of training on REDCap prior to usage of the system. Additional REDCap resources, including user guides and training videos, can be found on the REDCap website. See Section 5, “Training,” for additional details.

7. COUNTRY SITE (CS) SUPPORT

7. COUNTRY SITE (CS) SUPPORT

During a Country Site's (CS) participation in the Common Protocol, a periodic CS support visit (dependent on funding or for cause) will be completed by a RePORT International Coordinating Center (RICC) representative or designee. RICC and the Country Principal Investigator will take responsibility for protocol conduct and integrity of proposed country sites. The purpose of the visit will include the assurance of the specific points listed below, with a strong focus on the collaborative teaching opportunities for all involved in the visit. The visit will be an opportunity to provide protocol, technical, and regulatory support while fostering an open dialogue between the RICC representative(s) and the CS staff. During the visit, RICC representative(s) will confirm the following:

- The rights and safety of human participants are protected
- Resulting data are of the highest quality and integrity
- The study is implemented in compliance with the current approved version of the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, national and other regulatory requirements
- The reported study data are accurate, complete, and verifiable against adequate source documentation
- The staff and facilities are adequate for meeting the requirements of protocol implementation

7.1. What to Expect During the Visit

The RICC representative(s) will review CS protocol and regulatory adherence, perform an external quality assurance review, and support the administration and progress of the protocol on behalf of the funding organizations. The RICC representative(s) will be independent of the investigative staff conducting the research at the country networks/country sites and will not be employed or supervised by the CSs.

The RICC Representative(s) will:

- Ensure that the CS staff, including the Investigators, is conducting the study according to the protocol, GCP, and other regulatory requirements
- Verify that the data in the case report forms (CRFs) is in agreement with the source documents (source data verification)
- Review the accuracy and completeness of research records (e.g., regulatory and essential documents binder, CRFs, and other data collection tools, source data)
- Review other study-related activities for the funding organizations, such as study initiation activities, assessment of study facilities, etc.

8. REVISION HISTORY

Version	Date	Summary of Changes
1.0	03-26-2026	Original version of the MOP.