INTRODUCTION

Progress in tuberculosis (TB) clinical research is hampered by the lack of reliable biomarkers to serve as a surrogate endpoint predicting efficacy of prevention and treatment modalities unlike Human Immunodeficiency Virus (HIV) antiretroviral treatment research, which has greatly benefited from the HIV viral load biomarker. There is currently no substitute for sputum culture conversion for predicting efficacy of new candidate vaccines, drugs, and drug regimens and even culture is an imperfect predictor of drug or regimen efficacy. In addition, biomarkers that predict progression from latent to active disease are needed to advance TB prevention efforts, both in vaccine development and treatment for prevention. Lack of such scientific advances contributes to TB’s place as the single most common cause of death among individuals with HIV/AIDS, and the most common infectious cause of death in the world.

RePORT International began in 2012 as a cooperative strategy between the US NIH, DAIDS/NIAID and interested governments to address the threat of TB that affects the lives and well-being of people across the globe and which poses an increased risk for persons living with HIV or who are HIV infected. The initial RePORT International collaboration included TB research investigators from India collaborating with US-based TB research investigators, followed soon by addition of a newly formed Vanderbilt University (US) and Brazil consortium of TB researchers as well as a team of Indonesia investigators. Subsequently, a South Africa Medical Research Council TB research consortium was added (2016). The Bylaws are written to set clear guidelines and expectations for current and future groups to work together on a broad set of common goals.

RePORT INTERNATIONAL MISSION and PURPOSE

The purpose of RePORT International is to advance regional TB science which is also relevant in a global, international context; strengthen TB research capacity and infrastructure in high TB burden settings; and serve as an entity to foster research collaboration within each country and internationally, with the aim of carrying out a wide range of basic and clinical research that can lead to clinically important TB biomarkers, vaccines, drugs, and diagnostics.

GENERAL PRINCIPLES

RePORT International is a federation of independent RePORT consortia enrolling research participants in accordance with an agreed upon set of standards that are set forth in a Common Protocol which describes eligibility criteria, endpoint definitions, and the timing and methodologies for collection and storage of data and specimens. Each RePORT consortia is designed to support local, in-country TB-specific data collection, specimen bio-repositories, and local research. The standardized approach is expected to result in greater ease in sharing data and specimens across geographic regions, which should spur advances in important biomarker and other TB and TB-HIV research, while also building clinical research capacity in high-burden settings and increasing local access to quality data and specimens for members of each network and their domestic and international collaborators. Additional consortia and networks are expected to be added, helping to spur TB treatment and prevention research around the world.
Roles and Responsibilities of Sponsors

The National Institutes of Health, Institute of Allergy of Infectious Diseases, Division of AIDS (DAIDS) is the US government funding agency which provides overarching RePORT International oversight and support for the RePORT International Coordinating Center (RICC). DAIDS is responsible for:

1. Communicating the priorities and perspective of NIH, DAIDS/NIAID to the RICC and RePORT International co-sponsors and membership during annual meetings, Executive Committee teleconferences, and email communications as needed
2. Communicating in a timely manner any substantive changes anticipated in resources that might impact activities related to RePORT International research and functioning
3. Soliciting feedback from, and coordinating with the government sponsors of the various RePORT International consortia

Roles and Responsibilities of RICC

The RICC serves RePORT International investigators and the NIH, DAIDS/NIAID by working across all consortia and the TB research community to further TB research with the following expectations:

1. Provides both scientific and operational leadership for the Common Protocol (CP) and associated CP toolkit, including annotated case report forms (CRFs), RePORT International data elements bank, Manuals of Procedures (MOPs) as well as developing a RePORT International website to enable information sharing.
2. Assists new and existing consortia and consortia sites in harmonizing local or ‘parent’ protocols to align as closely as possible with the CP standard platform.
3. Coordinates cross-consortia activities and governance by convening leadership teleconferences, and an annual RePORT International conference that will serve as a global TB scientific meeting.
4. Obtains consensus from RePORT International membership on Bylaws to govern the collaborative research and resulting analyses and publications that come from RePORT International Partner work; forms committees and special interest groups as recommended by RePORT International members and Bylaws.
5. Facilitates RePORT International research by assisting in responses to external requests for proposals, or, when funds are available, by hosting internal funding opportunities to RePORT International Partners & investigators.
6. Upon request, works with RePORT International investigators in the context of independent or supplemental funding for specific sub-projects
7. Provides regular updates on recruitment and follow-up status and biological samples, to the RePORT International Partner consortia
8. Facilitates opportunities for RePORT International investigators to publish manuscripts, while working to ensure that all (the RICC, individual investigators, sponsors, collaborators) respect intellectual property and adhere to principles of authorship and publication as detailed by the International Committee of Medical Journal Editors (http://www.icmje.org/) and RePORT International Bylaws.

Roles and Responsibilities of Each RePORT Consortium
Each consortium is responsible for working toward the following expectations:

1. Affirm their commitment to the RePORT International bylaws and principles by signing the initial and any updated versions of the RePORT International Memorandum of Understanding.
2. Store and be prepared to share samples and data specified in the Common Protocol in a locally-established central repository and data management center, or stored locally under near-identical conditions, so as to facilitate intra- and inter-consortium analyses and research.
3. Establish local fair processes for sharing and storing clinical data and biological specimens among themselves, and with other RePORT investigators or teams.
   a. Develop processes that will enhance the quality and verifiability of data and biological samples collected by their sites, and stored in their data- and bio-repositories.
4. Work with the RICC to harmonize relevant study protocol, laboratory & biorepository procedures, data elements, data management and other key processes to align with the Common Protocol, data elements, manual of operations and biorepository standards, and annotating points of differentiation.
5. Provide to the RICC on a periodic (e.g., quarterly) basis:
   a. Common Protocol updates:
      i. Aggregate numbers enrolled, disaggregated by gender and drug-susceptibility pattern, when available, follow-up and study completion rates, as well as number and types of specimens in storage and available for analysis.
      ii. Samples (e.g., 10% of last quarter’s enrolled subjects) of de-identified data for quality evaluation and improvement.
   b. Updates on consortium-specific publications and presentations.
   c. Updated names and contact information of site PI’s and teams.
6. Participate in the annual RePORT International meeting and identifying representatives to serve on the RePORT International Steering Committee as well as other standing committees, including the Executive Committee (EC).
7. Seek opportunities, and cooperate with other Partner consortia members, to do cross-consortium research including utilizing data and specimens collected to further TB biomarker and other areas of interest.
   a. Of note: it is understood and agreed that investigators from each RePORT International Partner investigator has the primary right to, and control over, data and biological specimens collected during their own, non-Common Protocol, approved research.
8. Benefit from being a RePORT International Partner consortium by being eligible for RePORT-specific funding opportunities in addition to invited participation in annual RePORT International meetings and collaborative research.

**THE COMMON PROTOCOL AND TOOL KIT**

The Common Protocol (CP) and associated documents within the CP Toolkit serves as the platform for the standardized approach to be taken by RePORT International members, and that is to be implemented by all RePORT International CRUs. The CP is supported in each country by a biorepository, a data management center, and utilization of harmonized data elements and specimen collection standard operating procedures (SOPs). It is envisioned that this will provide TB researchers a
harmonized set of clinical data associated with biological specimens which will serve as a valuable resource to address important research questions in TB both locally and across sites.

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

Additional modules may be added to the CP to expand the scope of investigations. The procedures for developing and approving additional modules is [TBD]. Version control for the CP or additional modules will be maintained at the RICC and posted on the RePORT International website in a timely manner.

DATA AND SPECIMEN SHARING AND MANAGEMENT

Biological samples and individual research participant data collected as part of the RePORT International collaboration, will be stored in in each host country in a central repository and data management center, or stored locally under near-identical conditions, using tracking and storage conditions according to the RePORT International Manual of Operations, so as to facilitate cross-consortium analyses and research.

RePORT International has created a set of Common Protocol-defined data element definitions and formats, data structures and data curation procedures that RePORT sites are expected to use to allow for future data sharing. The RICC is responsible for maintaining these definitions and procedures, and for facilitating data sharing across consortia, assess and improve data quality and standardization over time. In order to accomplish this, the RICC will:

1) Maintain and update these tools, while educating and implementing them with the data management teams at each RePORT consortium

2) Develop, test and implement data transfer protocols with each consortium for a) proof of concept for consistency of data formatting and definitions for future cross consortium analyses, and b) for purposes of checking data completeness and quality. RICC will create periodic reports of data completeness and quality that will be shared with sites/consortia for quality improvement and will eventually be important to advocate for ongoing RePORT sponsor’s confidence and funding.
   a. Data use agreements between RICC and each consortium’s data management team will be in place before data are sent to RICC
   b. A sample (e.g., 10% of previous quarter’s enrolled subjects) of de-identified data will be requested from RePORT International consortia members on a regular basis using a specified, secure data transfer protocol, and will be analyzed for quality (e.g., completeness, consistency with expected data structure). These data will not be used for research, analysis or external publication.
3) Construct a database shell/structure consistent with the annotated case report forms and data element bank that will house both test data, and in preparation for cross-consortium data set sharing and analyses

It is expected that numerous cross-consortium RePORT International studies will be conducted over time. While each RePORT site or consortium may choose to directly share data with one another, it is anticipated that the RICC data management team will serve to collect and organize cross-consortium data into pre-specified data tables for RePORT Investigator analyses, as requested and agreed upon.

STRUCTURE AND FUNCTION OF REPORT INTERNATIONAL

Membership in RePORT International

A consortium or investigator from a single site is eligible to be included as a RePORT International Partner when meeting all the following entry criteria:

1. Intends to enroll a minimum of 250 adults and/or children with, or at risk for, active pulmonary TB, latent TB infection (and/or close contact to a case of active TB), in a prospective cohort, or other applicable research study.

2. Is a bona fide consortium that includes, or anticipates growing to include, 3 or more separate clinical research sites or units (CRUs), led by different site investigators, either within one country, or across multiple countries with a high burden of TB, TB-HIV or MDR TB, as defined by the WHO (http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf).

3. Consortia that are receiving funding or co-funding from the US NIH specifically for RePORT-related research are all considered eligible, as well as invited consortia receiving no US or NIH funding, but which agree to the principles set forth in the MOU and Bylaws.

4. The US NIH and/or Partner non-US governments may announce requests for proposals that are only available to co-funded Consortia, or have other restrictions. Such opportunities and accompanying restrictions will be made known in a transparent and fair manner to all RePORT International investigators.

Note, consortia or investigators engaged in TB clinical research who do not meet the RePORT International Partner consortium eligibility criteria, but who are interested in using the Common Protocol and package of tools for data and specimen harmonization, are welcome to do so and to propose collaborative research at any time. However, they will not be eligible for RePORT-specific funding opportunities that may become available.

Organizational structure

A. RePORT International Steering Committee

The Steering Committee serves as the central decision making body for RePORT International.

The Steering Committee comprises one voting member (representative) from each RePORT International site (i.e., clinical research unit [CRU]) and one voting member (representative) from their
US or other international collaborating partner, where relevant. The Steering Committee also includes one voting member (representative) from the RICC, and one voting member (representative) from each of the sponsors. Responsibilities of the Steering Committee:

1. Contribute to development of a scientific agenda
2. Vote on priorities for cross-consortium research concepts that involves use of data or specimens not described under a separate RFP or other funding mechanism
3. Receive and act upon timely updates on status of ongoing and new research ideas to encourage quality and timeliness of research projects
4. Vote to approve or disapprove research concepts approved by the EC. The Steering Committee will be notified of such other concepts disapproved.
5. Propose solutions to research barriers, unexpected findings or events

Officers of the Steering Committee

The Steering committee has a chair and a vice-chair. The chair is a voting member of, and elected by, the Steering Committee from one of the RePORT International sites. The vice-chair is the RICC Principal Investigator.

Terms of office for the Chair: Nominated from the Steering Committee at-large, followed by a secret vote tallied at the annual meeting, with runoff votes as needed to achieve a majority. The Chair serves a two-year term and can be re-elected once, for a total of 4 years. A person can be re-elected as Chair after a minimum 1-year hiatus.

B. RePORT International Executive Committee

1. Roles, responsibilities:
   a. Small group that works with the RICC, and on behalf of each Consortium, for day-to-day management of RePORT International
   b. Approximately monthly teleconferences plus in-person meetings when possible
   c. Review and vote on recommendations from the standing committees
   d. Communicate to the Steering Committee, as well as to their Consortia, standing committee and teams on a regular basis.
   e. Organize the agenda for each annual meeting
2. Membership:
   a. Chair and co-Chair of the Steering Committee, who will typically lead the monthly teleconferences and face-to-face meetings
   b. 2 representatives from each RePORT International Consortium, typically including 1 US and one non-US representative
   c. Chairs of the Standing Committees if different from the consortium representatives
   d. One representative from each Sponsor
3. Terms of office: The 2 representatives from each RePORT International consortium will be chosen by each Consortium according to their own governance rules. Each will serve a two-year term and can be re-elected once, for a total of 4 years. A person can be re-elected as a representative after a minimum 1-year hiatus. Note: For the first election only, by flip of a coin, one representative will serve 4 years instead of 3 to prevent complete change in Committee make-up at one time.
C. **Standing Committees**

Terms of office for each standing committee: Members will be nominated from the Steering Committee at-large, followed by a secret vote tallied at the annual meeting, with runoff votes as needed to achieve a plurality of votes (i.e., more votes than any other candidate). Each representative serves a two-year term and can be re-elected once, for a total of 4 years. A person can be re-elected after a minimum 1-year hiatus. Note: For the first election only, by flip of a coin, one representative will serve 3 years instead of 2, to allow overlap and to prevent complete change in Committee make-up at one time.

i. Initially, and every 2 years hence, each standing committee will determine a Chair and co-Chair, one of whom will attend each Executive Committee call and meeting. There are no term limits on Chairs and co-Chairs per se.

1. **Science Committee**
   a. Roles, responsibilities:
      i. Periodically review and recommend modifications to the Common Protocol or associated tools to keep pace with the field of TB scientific inquiry
      ii. Track ongoing cross-consortium studies – including stand-alone, separately funded projects – in terms of start-up, progress in enrollment, follow-up, analysis and publication, alerting the Executive Committee to significant problems
      iii. Identify important scientific opportunities as well as gaps in current knowledge and research questions amenable to pursuit by RePORT International collaboration
      iv. Review and recommend to the Executive Committee approval or disapproval of internal or external proposals for use of RePORT data or specimens when not part of a stand-alone, funded small grant or other project
         1. Recommendations will be accompanied by a description of the rationale for decisions made
         2. The Science Committee that reviews concepts that have merit may provide constructive feedback to assist the proposing authors in improving their proposal for re-consideration for as many cycles as the Science Committee deems practical and useful
         3. Track proposals from submission to approval, rejection or withdrawal (RICC can assist in this process)
      v. See Section XX for full process of EC followed by full SC voting on proposals
   b. Membership:
      i. There will be 2 RePORT International members on the Science Committee from each consortium, with no more than half being from US sites
      ii. The Steering Committee Co-Chair (PI for the RICC)
      iii. A representative from the Community Engagement committee
   c. Meeting frequency: Scheduled once-monthly at a minimum, more often as determined by the needs of the committee

2. **Publications Committee**
a. Role and responsibilities:
   i. The Publication Committee encourages timely and accurate dissemination of
      designs, methods, and results of research performed by RePORT International
      investigators; ensures a high standard of scientific quality; allows freedom for
      individual creativity; and appropriately acknowledges the efforts of professional
      persons involved in the planning, conduct, and analysis of cross-consortium
      RePORT International studies.
   1. Individual consortium publications and manuscripts (e.g., using RePORT
      South Africa-only data/specimens): The RICC is to receive – but not
      provide approval, or critical review and input, unless requested – peer-
      reviewed publications or manuscripts in press and will collate and
      review with the Publication committee periodically to determine
      optimal ways to best articulate the progress and potential of work being
      done by RePORT International.
   2. RePORT International cross-consortium manuscripts (e.g., using RePORT
      South Africa and India data/specimens) prepared for peer-reviewed
      publication or abstracts being submitted for potential presentation at
      international conferences: Investigators reporting on analyses involving
      data or specimens from more than one individual consortium are to
      submit manuscripts to the RICC for distribution to the Publications
      committee allowing 2 weeks for review, feedback and final approval for
      submission. The Committee will review for clarity and methodological
      soundness, and will encourage fair representation from contributors
      according to International standards (ICJME).

b. Membership of the P&P Committee
   i. There will be 2 RePORT International members from each consortium, with no
      more than half being from US sites
   ii. One member of the Community Engagement Committee.

c. Meeting frequency: Initial organizational call will be followed by calls as needed
   depending on submissions or other issues that arise. As much review and discussion as
   can be done by email is also acceptable.

3. Community engagement Committee [TBD]
   a. Roles and responsibilities
   b. Membership:

D. WORKING GROUPS
Working groups are long-term groups with specific interests, objectives and proposed tasks. Working
groups may be proposed by members of RePORT International or its committees. To be officially
recognized, the proposed working group should formulate a concept note for review by the Executive
Committee which, if approved, will forward to the Steering Committee for approval. Responsibilities:

1. Each Working group will determine its own schedule of calls or meetings, and will select a chair
to organize their interaction between and during face-to-face meetings.
2. Any interested member of RePORT International may join a WG
3. Working Groups may propose, or may be asked to give, a specific presentation at the annual
   meeting, although specific time on the plenary agenda may or may not be possible. They are
welcome to propose ideas or make recommendations to any standing committee, project or protocol development team at any time.

RePORT INTERNATIONAL REVIEW AND OVERSIGHT

Scientific Advisory Board (SAB)

The success of RePORT International relies upon access to the best ideas and leading edge concepts to support its overall mission, which is to build TB research capacity in high burden settings while creating repositories of carefully curated and stored data and specimens for TB biomarker and other clinically relevant research. To increase the likelihood of ongoing relevancy and success, a Scientific Advisory Board (SAB) will be assembled to provide independent advice and assessment.

The aim of the SAB will be to provide the RICC and other RePORT International senior decision-makers informed and objective opinions and advice.

SAB discussions will consist of both formal and informal components. The formal component will include periodic in-person or virtual meetings that will provide the RICC and RePORT International sponsors and leadership with an opportunity to engage external SAB members on a variety of pre-selected science-related topics relevant to RePORT International. SAB members may be asked to:

- Assess whether the RePORT International research agenda appears rigorous, globally relevant and of highest impact to the scientific and public communities represented.
- Review, discuss and reflect on the existing RePORT International body of work, and existing resources (i.e., data and specimens).
- Advise about the relevance and likely impact of the output from RePORT International consortia and investigators, and make recommendations about future direction and priorities.
- Consider critical or emerging science issues, planned science and research activities, and science communication.

Other requests of SAB may include:

- Give advice on the long-range strategy of RePORT International for achieving its mission to promote TB research specifically clinical / cohort / diagnostics / vaccines / drugs / transmission and as it informs basic science
- Make proposals for new research topics/programs, investigator competitions, and grants programs;

Local and Consortium-specific Institutional Review Boards (IRB)

a. Each site must hold a valid Federal-wide assurance (FWA) with the U.S. Office for Human Research Protections and must certify IRB approval for each nonexempt RePORT International-related research study in which the site is engaged.
b. Consortia are encouraged to use the same IRB or agree on one IRB to serve as the IRB of record for all sites, to streamline the process of initial and annual reviews.

c. The primary role of the IRB is to protect the rights and welfare of human participants in the research. In accordance with the United States Federal Regulations, an IRB may approve research only after it has determined that all of the following requirements are satisfied:

i. Risks to participants are minimized by using procedures that are consistent with sound research design, and that do not unnecessarily expose participants to risks, and whenever appropriate, researchers should employ procedures that are performed on participants for prevention, diagnostic or treatment purposes.

ii. Risks to participants are reasonable relative to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result from the research.

iii. The selection of participants is equitable taking into account the purposes of the research and the setting in which it is conducted. The protocol must be particularly attentive to the special problems that may arise when research involves vulnerable populations, such as children, pregnant women, fetuses, prisoners, mentally disabled persons, economically or educationally disadvantaged persons. If any of the participants are likely to be susceptible to undue influence or coercion, the protocol should provide additional safeguards in the study to protect such participants.

iv. Informed consent is sought from each prospective participant, or the participant's legally authorized representative, generally by means of a written consent document.

v. The research plan makes adequate provisions for monitoring the data collected to ensure the safety of participants.

vi. There are adequate provisions protecting the privacy of participants and maintaining the confidentiality of data.

d. When a study protocol is approved by the RePORT International Steering Committee, it is then ready for submission to each site or consortium IRB. Once approval is received, the RICC is to be informed for tracking and quality purposes.

e. Ongoing study protocols require continuing IRB review, at least annually, and approval by the appropriate IRBs.

**APPENDIX**

A. **RePORT International sites May 2017**

a. **MOU signed:** Brazil, South Africa, China

b. **MOU signature pending:** India, Indonesia

APPENDICES TO BE DEVELOPED
A. Process for approval of Common Protocol changes and other study or sub-study amendments, and informed consent amendments

B. Process for Evaluation and Approval of Cross-consortium Secondary Analysis
   a. Involving data only
   b. Involving data and specimen sharing

C. Publications Committee Policies and procedures

APPENDICES THAT MAY BE DEVELOPED IN THE FUTURE, AS NEEDED

A. Process for the development and approval of new RePORT International protocols
   a. Concept development and approval phase
   b. Protocol team selection and protocol development and approval

   Process for notification of and approval of externally funded projects involving all or a subset of RePORT International sites

---

1 The RICC was established in 2016 at FHI 360 in Durham, North Carolina. FHI 360 is a global nonprofit organization with over 40 years’ experience leading or managing global clinical and non-clinical research, including large, NIH-funded research networks.