SUPPLEMENT ARTICLE

RePORT International: Advancing Tuberculosis Biomarker Research Through Global Collaboration

Carol D. Hamilton,[1,2] Soumya Swaminathan,[3] Devasahayam J. Christopher,[4] Jerrold Ellner,[5] Amita Gupta,[6] Timothy R. Sterling,[7] Valeria Rolla,[8] Sudha Srinivasan,[9] Muhammad Karyana,[10,12] Sophia Siddiqui,[10] Sonia K. Stoszek,[11] and Peter Kim[9]

[1]Scientific Affairs, Global Health, Population and Nutrition, FHI 360, and [2]Department of Medicine, Division of Infectious Diseases, Duke University School of Medicine, Durham, North Carolina; [3]Department of Clinical Research, National Institute for Research in Tuberculosis, Chennai and Pune, and [4]Pulmonary Medicine, Christian Medical College, Vellore, India; [5]School of Medicine, Boston University, Massachusetts; [6]School of Medicine, Johns Hopkins University, Baltimore, Maryland; [7]Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee; [8]National Institute of Infectious Diseases Evandro Chagas–Fiocruz, Rio de Janeiro, Brazil; [9]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, [10]Collaborative Clinical Research Branch, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, and [11]Health Studies Sector, Westat, Rockville, Maryland; and [12]The National Institute of Research and Development, Indonesia Ministry of Health, Jakarta, Indonesia

Progress in tuberculosis clinical research is hampered by a lack of reliable biomarkers that predict progression from latent to active tuberculosis, and subsequent cure, relapse, or failure. Regional Prospective Observational Research in Tuberculosis (RePORT) International represents a consortium of regional cohorts (RePORT India, RePORT Brazil, and RePORT Indonesia) that are linked through the implementation of a Common Protocol for data and specimen collection, and are poised to address this critical research need. Each RePORT network is designed to support local, in-country tuberculosis-specific data and specimen biorepositories, and associated research. Taken together, the expected results include greater global clinical research capacity in high-burden settings, and increased local access to quality data and specimens for members of each network and their domestic and international collaborators. Additional networks are expected to be added, helping to spur tuberculosis treatment and prevention research around the world.

Keywords. tuberculosis; biological markers; biological specimen banks; prospective studies; specimen handling.

Tuberculosis remains one of the most significant infectious causes of mortality and morbidity worldwide, and is the number-one cause of death among those infected with human immunodeficiency virus (HIV). One of the major research needs is to find biomarkers that accurately predict outcomes of active and latent tuberculosis (LTBI), to facilitate development of better treatment and prevention interventions. To meet this need, the US National Institutes of Health (NIH) is working with interested governments to provide a platform for coordinated and collaborative approaches to tuberculosis research. These partnerships comprise a consortium called RePORT International.

Currently, RePORT consortia are being established in India, Brazil, and Indonesia, and discussions are under way in South Africa as well. Each reflects national research goals, but are coordinated through utilization of common standards and practices, including a RePORT International Common Protocol with corresponding case report forms and manual of operations developed in collaboration with investigators in the various consortia. Data and biospecimen repositories are being developed in each country to store their own data and samples. This platform sets the stage for future combined or comparative data analyses, and should be an invaluable resource for in-country and cross-national collaborations between bench and clinical researchers. We report here the current composition of RePORT International, details about the Common Protocol, and ideas for the future.

Correspondence: Carol D. Hamilton, MD, Global Health, Population, and Nutrition, FHI 360, 359 Blackwell St, Durham, NC 27701 (chamilton@fhi360.org).

Clinical Infectious Diseases® 2015;61(S3):S155–9
© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/civ611

INDIVIDUAL COUNTRY COHORTS

India

RePORT India is a joint venture between the Indian and US governments. The Indo-US Vaccine Action Program, a collaboration between the Indian Department of Biotechnology, the Indian Council of Medical Research, and the US NIH, is cofunding 5 teams of India- and US-based investigators to implement individual cohort studies of active and latent tuberculosis in India. Investigators are funded to enroll subjects into their own parent protocol. Eligible subjects from each parent protocol will be asked to coenroll into the RePORT International Common Protocol. All subjects will be enrolled from the sites in India, and are expected to enroll up to 5500 active tuberculosis cases and 14 000 LTBI household contacts of active tuberculosis cases in their parent protocols (Table 1). The sites are all experienced in tuberculosis clinical research, represent a mix of urban and rural, geographically disparate populations, and bring unique interests and expertise to their parent projects.

The specific sites comprising RePORT India include the M.V. Diabetes Research Centre in Chennai, working with US partners at the University of Massachusetts to study the impact of diabetes on tuberculosis severity among adults; Byramjee Jeejeebhoy Medical College in Pune and the National Institute for Research in Tuberculosis (NIRT) in Chennai, working with US partners at Johns Hopkins University to investigate host and microbial factors associated with active and latent tuberculosis infection in adults and children; Blue Peter Public Health & Research in Hyderabad, working with the University of Texas Health Science Center to study the role of cellular immunity in preventing progression to active tuberculosis; Jawaharlal Institute of Postgraduate Medical Education and Research in Puducherry, working with Boston University Medical Center to study risk factors for treatment relapse and progression to active tuberculosis; and Christian Medical College in Vellore, working with the University of Washington to study the impact of adjunctive steroids for tuberculous meningitis.

An Executive Committee has been constituted to provide leadership, governance, and guidance for the RePORT-India consortium. The consortium is also supported by a central biorepository housed at the NIRT in Chennai, and a central data management center housed at the Society for Applied Studies–Centre for Health Research and Development in Delhi.

Brazil

RePORT Brazil is a joint venture between the Brazilian and the US governments. The Brazilian Ministry of Heath, Department of Science and Technology (DECIT) and the US NIH are cofunding a team of Brazil- and US-based investigators to enroll persons with active and latent tuberculosis in Brazil. Four sites in Rio de Janeiro, 1 site in Manaus, and 1 site in Salvador were selected to enroll up to 900 active tuberculosis cases and 2700 close contacts of those tuberculosis cases (Table 1). Vanderbilt University is the US-based academic partner working with RePORT Brazil. RePORT Brazil is led by a scientific and steering committee composed of researchers and members of NIH and DECIT who will provide leadership, governance, and guidance to the consortium.

RePORT Brazil consortium sites also represent a diverse population, but in contrast to RePORT India will be enrolling into a single protocol that is harmonized with the RePORT International Common Protocol. Sites will recruit sputum culture–positive adults to observe the outcome of tuberculosis patients as well as the occurrence of tuberculosis among contacts with and without evidence of latent tuberculosis. Persons with latent tuberculosis will be offered isoniazid per Brazilian guidelines, whereas those who are tuberculin skin test (TST) or interferon-γ release assay (IGRA) negative will not receive treatment. The RePORT Brazil biorepository will be in Salvador at the Instituto Brasileiro de Reabilitação.

Indonesia

RePORT Indonesia will be a part of the ongoing government-to-government partnership between the US NIH and the Indonesia NIHRD (National Institute of Health Research and Development). Indonesia will collaborate with the consortium through the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) network. This existing partnership between the 2 governments supports a network of 9 academic and research institutions and hospitals to conduct research on infectious diseases and is currently conducting research on

Table 1. Expected Enrollments and Outcomes by Consortium

Category	India	Brazil	Indonesia
Anticipated patients with active tuberculosis	5500	900	500
Anticipated relapse or failure among subjects with active tuberculosis	275–550	45–90	35
Anticipated household contact/subjects with latent tuberculosis	14 000	2700	Not enrolling at this time
Anticipated cases of tuberculosis among household contacts/subjects with latent tuberculosis	1300–2500	54–540	

febrile illness in Indonesia. The Indonesian Ministry of Health has identified tuberculosis as a national priority disease area.

The Indonesia network has developed a study that will enroll 1000 presumptive new tuberculosis cases and 357 previously treated cases. Like RePORT Brazil, the parent study has been harmonized with RePORT International Common Protocol to harmonize collection of data and biospecimens using standardized methods and agreed-upon time points. Patients with drug-susceptible and multidrug-resistant disease will be followed from commencement to end of treatment for drug-sensitive patients and 2 years for MDR patients. Indonesia is considering expanding the study to include household contacts of active cases.

THE COMMON PROTOCOL

The RePORT International Common Protocol standardizes methods for collecting clinical data and biological specimens for banking and provides a priori definitions for key tuberculosis outcomes while ensuring that appropriate specimens and data are collected to document these outcomes. The guiding principles include simplicity and standardization to help maximize Common Protocol relevance wherever it is implemented throughout the world.

A recent consensus statement about tuberculosis biomarker development and expert consultations served in determining the basis for types of specimens to collect [1, 2]. The specimens required for collection are the least "simple" aspect of the study, as we try to anticipate what might be the most useful future biomarkers research. The Common Protocol uses standardized (although not necessarily Clinical Data Interchange Standards Consortium–validated) tuberculosis data elements as much as possible [3] and is patterned on the Global TB Alliance's Consortium for Tuberculosis Biomarkers (CTB^2) protocol to encourage future data sharing [4].

Of special interest to RePORT International is to collect biological specimens that can lead to biomarkers that are also relevant to the pediatric population, such as those that may predict severe disseminated diseases, or extrapulmomary vs pulmonary disease. Confounding these efforts are the difficulties associated with gold-standard diagnosis of tuberculosis in children. To address this, we have adopted pediatric case definitions based on published guidelines in an attempt to provide both rigor and standardization to the difficulties in pediatric tuberculosis diagnosis [5]. In addition, the RePORT International team is working with the NIH-convened Pediatric Biomarkers Working Group to develop a set of standards for specimen collection and processing that should also lead to optimized pediatric data. A "toolkit" of recommended laboratory procedures, annotated case report forms, a data elements bank, a manual of procedures, a chest radiograph scoring system, and data transfer specifications are being developed to promote data compatibility and procedural harmonization. To ensure that the collected data and specimens are of the highest quality, each RePORT site has been provided clinical and laboratory support through site visits, they have established quality assurance systems, and they conduct protocol, laboratory, and chest radiograph trainings for site staff.

The RePORT International Common Protocol comprises 2 separate prospective cohorts, 1 enrolling subjects at the time of diagnosis of active pulmonary tuberculosis disease (cohort A) and the second enrolling household contacts to an active tuberculosis case (cohort B). Adults and children are eligible for enrollment in each group. Active tuberculosis cohort participants must be culture confirmed (adults) or meet specific clinical criteria (children); household contact cohort participants may or may not have evidence of latent tuberculosis (IGRA or TST positive). Key cohort A outcomes are treatment failure (defined as persistent tuberculosis disease despite ongoing treatment) and relapse (defined as recurrent tuberculosis disease after completion of a full therapeutic regimen). The main cohort B outcome is development of active tuberculosis.

Cohort A will collect biological specimens plus clinical data at baseline (before or within 1 week of treatment initiation), at months 1 and 2, at treatment completion, and at 6 months after treatment (Table 2). We anticipate that specimens from these time points will provide a continuum of inflammatory and immunologic responses spanning a time of highest bacillary burden to cured tuberculosis disease. Participants will be assessed for outcomes (eg, cure, failure or relapse, death) at each follow-up visit. We anticipate detecting >90% of all relapses by following the cohort for this time period [6] and for the current RePORT groups combined, we anticipate between 300 and 700 relapse or failure events in the active tuberculosis cohort, assuming the majority of parent protocol participants coenroll into the RePORT International Common Protocol.

Cohort B will collect samples and clinical data at baseline (within 6 months of exposure to an adult with active tuberculosis) and 6, 12, and 24 months later (Table 2). Specimens will be saved from all those who develop the outcome of interest—active tuberculosis—and from a subset of subjects who do not. Participants who develop active tuberculosis will be encouraged to enroll in cohort A. We anticipate the 24-month follow-up will allow us to detect >90% of all cases of latent tuberculosis that progresses to active tuberculosis [7], leading to between 1350 and 3000 events with the current Consortium, again assuming the majority of parent protocol participants coenroll into the RePORT International Common Protocol.

A few key points about the Common Protocol and in-country specimen and data storage:

- It is designed to provide prospectively collected data and biological specimens to address important hypothesis-driven questions about active and latent tuberculosis, and hopefully

Table 2. Data and Specimens Collected in the Common Protocol

Protocol	Active TB Cohort	Household Contact Cohort
Schedule of visits	Baseline, month 1, month 2, end of treatment, 6 mo posttreatment, and in the event of failure or relapse	Baseline, months 6, 12, and 24, and in the event of suspected or confirmed development of active TB
Data collected for prognostic and epidemiological analyses	CXR, HIV (CD4+), HbA1C, IGRA, or TST, BCG vaccine history, sputum smear, and cx/DST	IGRA or TST; for those who develop active TB: HIV, CBC, HbA1C
Specimens collected for future biomarker research	IGRA supernatants, *Mtb* isolate, whole blood (PAXgene + PBMCs + genotyping), plasma, urine, sputum, saliva. For those who develop TB relapse or failure: new *Mtb* isolate, sputum	IGRA supernatants, whole blood (PAXgene + PBMCs + genotyping), plasma, urine. For those who develop active TB: *Mtb* isolate, sputum
Types of epidemiological data collected	Demographics, clinical signs and symptoms, socioeconomics, tobacco and alcohol use	Same as active TB cohort
Total follow-up	12 mo for drug-susceptible and ~24 mo for MDR TB (6 mo after end of treatment for all)	24 mo. In-person follow-up is preferred, but telephone follow-up allowed

Abbreviations: CBC, complete blood count; cx, culture; CXR, chest radiograph; DST, drug susceptibility testing; HbA1C, hemoglobulin A1C; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; MDR, multidrug-resistant; *Mtb*, *Mycobacterium tuberculosis*; PBMC, peripheral blood mononuclear cell; TB, tuberculosis; TST, tuberculin skin test.

to assist in development of prognostic biomarkers, although the protocol itself does not prespecify a set of analyses.

- Case report forms have been harmonized as much as possible across the first 3 consortia, but are adaptable for local requirements. For example, it is expected that all sites will use a case report form collecting the same demographic, medical, and social information. However, attempts to quantify tobacco use (eg, bidis in India, cigarettes in Brazil) or race and ethnicity (eg, by mother tongue in India, by racial heritage in Brazil) require local customization. We have established a list of "required" vs "ideal" data elements, specimens, and time points to guide consortium members.
- It has been agreed upon at the onset that each host country or host country consortium has the financial resources to ensure adequate storage and retrieval capacity for biological specimens either in a central facility, or in a curated decentralized system.
- Each consortium will determine its own data management strategy—centralized or site-based—but agree to use standardized reporting format and data structures so that data can be pooled for cross-site, cross-consortia analyses.

DISCUSSION: VISION FOR THE FUTURE

The need to elucidate biomarkers relevant to the treatment and prevention of tuberculosis is a priority that is shared broadly by the tuberculosis research field and has the potential to significantly impact not only research but clinical practice globally. When data amassed showing that HIV viral load accurately predicted subsequent immunologic and biologic outcomes (eg, development of opportunistic infections and mortality) [8, 9], the pathway for therapeutic trials of new drugs and drug combinations became much more efficient and provided a cost-effective way to measure the effectiveness of HIV treatment at the individual patient level. Tuberculosis research needs similar surrogate biomarkers, which accurately and promptly predict key active or latent tuberculosis outcomes. We believe that RePORT International will help achieve that goal while also increasing clinical research capacity in high-burden settings, enabling rigorous multicenter clinical trials for drugs, diagnostics, and vaccines to proceed with greater speed and efficiency.

We also anticipate that RePORT consortia will provide an important mechanism for addressing regional research priorities such as collecting effectiveness data when new treatment or prevention strategies are rolled out in high-burden settings. Differences in toxicities, relapses, and successes, for example, can be correlated with differences in population genetics, nutritional status, and prescribing practices, thereby providing critical information to guide local treatment programs. Furthermore, the standardized structures comprising the basis of RePORT International will facilitate South–South collaborations and foster collaborative approaches that will allow leveraging of regional research to address global priorities. We hope that this model of research will increase the influence and ability of local research funders and investigators to advance research that is of local importance while expanding the capacity for international studies.

Challenges that RePORT International will face include how to cost-effectively monitor data and specimen quality to ensure quality standards are maintained, manage in-country regulations that tend to restrict data and specimen sharing, and be aware of differences in local standards of care for treatment and prevention. We expect to mitigate the quality issues by creating quality assurance tools and expectations for consortium members, while using clearly articulated data and specimen use agreements at the outset to facilitate sharing.

A future RePORT International coordinating center is being created that will facilitate communication between RePORT networks, and will develop, maintain, curate, and evolve RePORT Standards and standard operating procedures, advance multiregional/international scientific priorities via facilitating rapid presentation and dissemination of data, host scientific workshops, and coordinate research efforts where necessary. It is hoped that this multinational collaboration will advance tuberculosis research in the early 21st century.

Notes

Financial support. For the efforts of Westat and its subcontract with FHI360, this project has been funded in whole or in part with federal funds from the US Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Department of Health and Human Services, under the contract "NIAID HIV and Other Infectious Diseases Clinical Research Support Services (CRSS)."

The Regional Prospective Observational Research in Tuberculosis (RePORT) India work is supported by the Indian Department of Biotechnology, the Ministry of Science and Technology, and the Indian Council of Medical Research, with cofunding by the US Office of AIDS Research and the US NIAID. The RePORT Brazil work is supported by Brazil's Ministry of Health and Department of Science and Technology, with cofunding by the US Office of AIDS Research and the US NIAID. The RePORT Indonesia work is supported by the Indonesia National Institute of Health Research and Development and the US NIAID.

Supplement sponsorship. This article appears as part of the supplement "Advances in Tuberculosis Research: A Blueprint for Opportunities." This article was sponsored by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Potential conflicts of interest. A. G. has received grants from NIH, Centers for Disease Control and Prevention, Ujala Foundation, Gilead Foundation, Mylan, and World Health Organization. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Wallis RS, Kim P, Cole S, et al. Tuberculosis biomarkers discovery: developments, needs, and challenges. Lancet Infect Dis **2013**; 13:362–72.
2. Nahid P, Saukkonen J, Mac Kenzie WR, et al. CDC/NIH workshop. Tuberculosis biomarker and surrogate endpoint research roadmap. Am J Respir Crit Care Med **2011**; 184:972–9.
3. McCourt B, Harrington RA, Fox K, et al. Data standards: at the intersection of sites, clinical research networks, and standards development initiatives. Drug Inf J **2007**; 41:393–404.
4. TB Alliance. Innovations: discovery of biomarkers (CTB2). Available at: http://www.tballiance.org/pipeline/innovation-detail.php?id=2. Accessed 9 August 2015.
5. Marais BJ, Graham SM, Cotton MF, Beyers N. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis **2007**; 196(suppl 1):S76–85.
6. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med **2011**; 365:2155–66.
7. Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet **2002**; 360:528–34.
8. O'Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. Ann Intern Med **1997**; 126:939–45.
9. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med **1997**; 126:946–54.