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Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH): protocol for a multicentric prospective observational study

Akshay Gupte,[1,2] Chandrasekaran Padmapriyadarsini,[3] Vidya Mave,[2,4] Dileep Kadam,[5] Nishi Suryavanshi,[4] Shri Vijay Bala Yogendra Shivakumar,[3] Rewa Kohli,[4] Nikhil Gupte,[2,4] Kannan Thiruvengadam,[3] Anju Kagal,[5] Sushant Meshram,[5] Renu Bharadwaj,[5] Sandhya Khadse,[5] Geetha Ramachandran,[3] Luke Elizabeth Hanna,[3] Neeta Pradhan,[4] N S Gomathy,[3] Andrea DeLuca,[1,2] Amita Gupta,[1,2] Soumya Swaminathan,[6] on behalf of the CTRIUMPH Study Team

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PC, VM, AG and SS contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Amita Gupta;
agupta25@jhmi.edu

ABSTRACT

Introduction: Tuberculosis disease (TB) remains an important global health threat. An evidence-based response, tailored to local disease epidemiology in high-burden countries, is key to controlling the global TB epidemic. Reliable surrogate biomarkers that predict key active disease and latent TB infection outcomes are vital to advancing clinical research necessary to 'End TB'. Well executed longitudinal studies strengthening local research capacity for addressing TB research priorities and advancing biomarker discovery are urgently needed.

Methods and analysis: The Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH) study conducted in Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune and National Institute for Research in Tuberculosis (NIRT), Chennai, India, will establish and maintain three prospective cohorts: (1) an Active TB Cohort comprising 800 adults with pulmonary TB, 200 adults with extrapulmonary TB and 200 children with TB; (2) a Household Contact Cohort of 3200 adults and children at risk of developing active disease; and (3) a Control Cohort consisting of 300 adults and 200 children with no known exposure to TB. Relevant clinical, sociodemographic and psychosocial data will be collected and a strategic specimen repository established at multiple time points over 24 months of follow-up to measure host and microbial factors associated with (1) TB treatment outcomes; (2) progression from infection to active TB disease; and (3) *Mycobacterium tuberculosis* transmission among Indian adults and children. We anticipate CTRIUMPH to serve as a research platform necessary to characterise some relevant aspects of the TB epidemic in India, generate evidence to inform local and global TB control strategies and support novel TB biomarker discovery.

Ethics and dissemination: This study is approved by the Institutional Review Boards of NIRT, BJGMC and Johns Hopkins University, USA. Study results will be disseminated through peer-reviewed journals and research conferences.

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Strengths and limitations of this study

- Well-characterised clinical cohorts of active tuberculosis cases and their at-risk contacts.
- Prospective follow-up with robust and clinically relevant outcome assessment.
- Strategic bio-banking of key specimens prospectively linked with clinical data.
- The ambitious nature of the study may threaten completeness of data.

BACKGROUND

Mycobacterium tuberculosis (Mtb) is among the most important infectious agents worldwide. An estimated 9 million people developed tuberculosis disease (TB) and 1.5 million died from the disease globally in 2014.[1] Over 2 billion people are infected with Mtb and are at risk of progressing to active disease.[1] An effective and evidence-based response to TB, particularly in high-burden countries, is key to controlling the global TB epidemic.

With 40% of its 1.2 billion people infected and 2.3 million people developing active disease each year, India accounts for approximately one-fourth of the global burden of TB.[1 2] The epidemiology of TB in India

differs from that in other high-burden countries warranting evidence-based interventions relevant to these settings. For instance, the phylogeography of Mtb strain lineages—and therefore virulence and transmissibility—differs significantly between India, sub-Saharan Africa and the Americas.[3–6] Furthermore, while a vast majority of TB cases in sub-Saharan Africa are HIV co-infected, only 5% of TB in India is associated with HIV.[1 2] Conversely, diabetes mellitus (DM)—while increasing the risk of TB only threefold compared to 22 times for HIV—accounts for nearly 20% of all smear positive cases making it a more relevant risk factor in the Indian setting.[7 8] Similarly, the high prevalence of poverty, air pollution (AP) exposure, undernutrition, smoking and alcohol consumption may further fuel the TB epidemic.[9–15] Despite the enormous burden, our knowledge of the relative importance of key risk factors, as well as the potential of targeted interventions necessary for a population-level impact on the TB epidemic, remains in its infancy. Comprehensive assessments of prevailing host and microbial factors impacting outcomes of TB treatment, progression from infection to active disease, and recurrence are critical to reducing TB in the Indian setting.

The WHO's new End TB Strategy calls for a 90% reduction in TB incidence and 95% reduction in TB deaths between 2015 and 2035.[16] However, the incidence of TB is falling at less than 2% per year; making it difficult to achieve these ambitious goals.[1] Innovative approaches targeting all stages of TB—transmission, progression and treatment—are needed to end TB as a global public health problem. However, progress in TB clinical research is hampered due to the absence of reliable biomarkers that predict progression from infection to active disease, treatment failure and relapse. Well-characterised clinical cohorts that can link host and microbial biomarker discovery to relevant latent and active TB outcomes are needed to develop better treatment and preventive interventions.[17 18]

The Cohort for Tuberculosis Research by the Indo-US Medical Partnership (CTRIUMPH) study funded by the National Institutes of Health (NIH), USA and the Department of Biotechnology (DBT), India, Indo-US Vaccine Action Programme (VAP) Initiative on TB Research was established to address knowledge gaps in our understanding of the TB epidemic in India and to advance TB biomarker discovery. In this manuscript, we provide a brief overview of the design, methods and scope of the CTRIUMPH study.

METHODS

Goals and objectives

The overarching goal of the CTRIUMPH study is to develop a well-characterised cohort of patients with TB and high-risk contacts with robust clinical data and a comprehensive specimen repository. Such a cohort will have transformative potential to offer insights into TB treatment response, disease progression and transmission. We will establish and maintain three prospective cohorts: (1) an Active TB Cohort comprising 1200 adults and children with TB, (2) a Household (HH) Contact Cohort of 3200 adults and children at risk of developing active disease and (3) a Control Cohort consisting of 500 adults and children with no known exposure to TB. At two heterogeneous study sites, CTRIUMPH will address three primary aims: (1) measure host and microbial factors associated with treatment outcomes; (2) investigate host and microbial factors associated with progression from infection to active TB disease; and (3) explore host and microbial factors associated with Mtb transmission.

Study design and setting

The CTRIUMPH study is a 5-year prospective cohort study ongoing at Byramjee Jeejeebhoy Government Medical College (BJGMC) and the National Institute for Research in TB (NIRT) in India since August 2014, through academic and operational partnerships with the Center for Clinical Global Health Education and the Center for TB Research at Johns Hopkins University (JHU), USA. BJGMC is located in Pune city, which is a predominantly urban metropolis (population of approximately 5 million). BJGMC is affiliated with Sassoon General Hospitals (SGH), a tertiary public hospital evaluating approximately 4500 TB suspects annually. The BJGMC study site will enrol active TB cases from SGH as well as referrals from Revised National Tuberculosis Control Programme (RNTCP) clinics in the city. RNTCP estimated TB incidence and prevalence in Pune at 185 and 220 per 100 000, respectively.[2] The population presenting to BJGMC is predominantly urban/peri-urban (88%) with a median household income of US$1200 per year. BJGMC-specific data estimates prevalence of HIV co-infection, DM, tobacco exposure and undernourishment among TB cases to be 15%, 20%, 40% and 50%, respectively. NIRT, located in Chennai, will enrol active TB cases from two RNTCP clinics in the Tiruvallur district. Tiruvallur is a predominantly rural area (population approximately 3.4 million). Approximately 1500 TB suspects are evaluated by the RNTCP TB units (TU's) at Velliyur and Poonamalle annually. RNTCP estimated TB incidence and prevalence in Tiruvallur at approximately 120 and 125 per 100 000, respectively.[2] The population presenting to NIRT is predominantly rural and NIRT-specific data estimates prevalence of HIV co-infection among TB cases at 5%.

Study population

The Active TB Cohort will comprise adults and children with newly diagnosed pulmonary TB (PTB) or extrapulmonary TB (EPTB) living within a 50 km radius of the study sites. TB cases who have received antituberculosis treatment (ATT) in the past, those who are on ATT for more than 7 days for current illness, or those who do

not consent to home visits for enrolling their HH contacts will be excluded. Our first aim—to identify host and mycobacterial factors associated with TB treatment outcomes—will be addressed in this cohort. The Active TB Cohort will enrol and evaluate 800 adults with PTB, 200 adults with EPTB and 200 children with TB over a 5-year study period.

The purpose of establishing the HH Contact Cohort is to explore host and microbial factors associated with Mtb transmission, and progression from infection to active TB disease (aims 2 and 3). Up to 3200 HH contacts of enrolled adult PTB cases in whom active TB has been ruled out will be enrolled and evaluated in the HH Contact Cohort. We define HH contacts as adults and children living in the same house as the index case during the 3 months prior to diagnosis of the Index cases' TB. Evidence of Mtb infection will not be required for enrolment into the HH Contact Cohort. Additionally, HH contacts who have active TB at entry and those who develop TB during their follow-up will be offered enrolment into the Active TB Cohort.

Randomly selected households within a 5 km radius of the Active TB Cohort participant's household will be approached for enrolment into the Control Cohort. The Control Cohort, with similar geographic and epidemiological characteristics as the Active TB and HH Contact Cohorts, will serve as a comparison group for exploratory biomarker studies. Up to 300 adults and 200 children with no known exposure to an active TB case will be offered enrolment into the Control Cohort.

Study procedures

Active TB Cohort participants will be evaluated at the study clinic or in a mobile medical van during ATT (Entry, 2 weeks, 4 weeks, 2-month, 5-month, 6-month/End of Treatment visits) and up to 18 months following ATT completion (12-month, 18-month, 24-month visits) to identify factors associated with TB treatment outcomes. HH Contact Cohort participants will be evaluated in their homes, study clinic or a mobile medical van for 24 months (Entry, 4–6-month, 12-month, 18-month, 24-month visits) to identify factors associated with Mtb transmission and progression to active TB. Control Cohort participants will be evaluated in their homes for 12 months (Entry, 4-month, 12-month visits). Relevant clinical and epidemiological data (table 1) will be prospectively collected and a carefully collected specimen repository established (table 2) for biomarker discovery at select study visits for all three cohorts.

Specimen handling and storage

Whole blood will be collected, aliquoted and stored at −80°C or −150°C in PAXgene tubes for host RNA extraction, EDTA tubes (BD Biosciences) for genetic analysis, QGIT tubes (QIAGEN, Germany) for supernatant extraction and CPTTM tubes (BD Biosciences) for plasma and PBMC extraction. Sputum and subcultures of Mtb isolates will be processed, aliquoted and stored in cryo-containers at −80°C. Urine samples will be collected, aliquoted and stored at −80°C. Approximately 30 strands of hair will be isolated from the occipital region according to standardised hair-collection methods and stored.[19] PBMC samples will be stored in liquid nitrogen containers and additional aliquots may be transported to the central biorepository at NIRT for long-term storage. Samples may be stored up to 15 years following study completion. Sample aliquots will be made available to study researchers and their collaborators following a review of proposed scientific work by study investigators and the leadership team.

Study outcomes

Active TB Cohort participants will be evaluated up to 24 months following ATT initiation for unfavourable treatment outcomes of failure, recurrence or death. Treatment failure will be defined microbiologically (culture confirmed TB by the end of ATT), or clinically (persistence, progression or recurrence of signs and symptoms highly suggestive of TB disease in the absence of an alternate diagnosis) if a microbiological diagnosis of failure or cure cannot be established. TB recurrence will be defined microbiologically (culture confirmed TB), or clinically (radiological evidence or signs and symptoms suggestive of TB disease) during the follow-up period after ATT completion if a microbiological diagnosis of recurrence cannot be established (table 3). We will evaluate secondary outcomes of time to sputum acid-fast bacilli (AFB) negativity, time to culture negativity and time to detection of Mtb using mycobacterial growth indicator tubes (MGIT).

HH Contact Cohort participants will be evaluated for up to 24 months following enrolment for incident Mtb infection and progression to active TB. Incident Mtb infection will be defined as conversion of the tuberculin skin test (TST) or Quantiferon Gold in Tube assay (QGIT), or a positive TST or QGIT at entry for children under 5 years. Incident TB cases in the HH Contact Cohort will be identified by microbiological confirmation for adults and international consensus TB case definitions for suspected paediatric TB cases[20] (table 3). Secondary outcomes for this cohort will include proportion with co-prevalent TB at entry, and proportion of HH contacts with identical DNA fingerprints as their index cases.

Statistical considerations

Aim-1: To measure host and microbial factors associated with TB treatment outcomes. The primary analysis set will comprise 800 adults with PTB. The primary outcome will be poor treatment outcome defined as failure, recurrence or death. Host factors including age, sex, DM, HIV, AP exposure, tobacco exposure and malnutrition will be key risk factors for poor treatment outcomes. Person years of follow-up will be calculated for each member of the analysis set. Crude treatment failure rates and 95% exact Poisson CIs in the presence

Table 1 Evaluations performed in the CTRIUMPH study

	Demographic and psychosocial evaluation	Clinical assessment	Laboratory evaluation
Active TB Cohort (n=1200)	Socioeconomic status Health-seeking behaviour Alcohol consumption Smoking history Secondhand smoke exposure HRQOL Household food insecurity Medication adherence Objective AP assessments	Medical history* Medication history† Targeted physical examination Anthropometry Lung Health assessments	AFB microscopy Mycobacterial culture and DST Xpert MTB/Rif Histopathology for EPTB HIV test and CD4 enumeration Liver function tests HbA1c, CBC Urine pregnancy test Chest X-ray Population PK for 1st-line drugs Sputum microbiome analysis
HH Contact Cohort (n=3200)	Health-seeking behaviour Alcohol consumption Smoking history Secondhand smoke exposure HRQOL Medication adherence Objective AP assessments	Medical history* Medication history† Targeted physical examination Anthropometry Exposure gradient Lung Health assessments	AFB microscopy Mycobacterial culture and DST TST and QGIT HIV test and CD4 enumeration HbA1c CBC Urine pregnancy test Chest X-ray
Control Cohort (n=500)	Socioeconomic status Health-seeking behaviour Alcohol consumption Smoking history Secondhand smoke exposure HRQOL Household food insecurity Medication adherence	Medical history* Medication history Targeted physical examination Anthropometry	TST and QGIT HIV test and CD4 enumeration HbA1c, CBC Urine pregnancy test Chest X-ray

*Includes history of BCG vaccination and previous TST or Interferon γ release assay testing.†Includes history of current or previous isoniazid prophylaxis.
AFB, acid-fast bacilli; AP, air pollution exposure; ATT, antituberculosis treatment; CBC, complete blood count; DST, drug sensitivity testing; EPTB, extrapulmonary TB; HbA1c, glycated haemoglobin for DM; HH, household; HRQOL, Health-Related Quality of Life; n, Target sample size; PK, pharmacokinetics; QGIT, Quantiferon Gold in Tube; TST, tuberculin skin test.

and absence of primary risk factors will be calculated. Adjusted treatment failure rate ratios will be estimated using multivariate Poisson regression models with person-years of follow-up as an offset. The Poisson regression models will also investigate interaction between individual and HH factors that might influence treatment outcomes. We expect that 20% (n=160) of 800 adult PTB cases will have the composite primary outcome (2% will fail, 6% will die and 12% will have recurrence). Assuming a 10% loss to follow-up, this study will have at least 90% power at 5% level of significance to identify risk factors, with a prevalence of 10% to 40%, associated with poor treatment outcomes with a treatment failure risk ratio ranging from 1.5 to 6.0 over 24 months of follow-up. A secondary analysis set, comprising 200 adults with EPTB and 200 paediatric TB cases, will most likely be underpowered to detect a meaningful association between primary risk factors and poor treatment outcomes.

Aim-2: To investigate host and microbial factors associated with progression from infection to active TB disease. The analysis set will be 3200 HH contacts of 800 adult PTB cases, assuming four HH contacts in every Index case HH. The primary outcome will be diagnosis of active TB among individual HH contacts within 24 months of follow-up. Index PTB cases from the Active TB Cohort will form clusters and individuals within the HH of the index case are correlated. The association between host and microbial factors with progression from infection to active TB disease will be estimated using random effects Poisson regression models, with index cases as random effects to address correlation of individuals within a household. Incident rate ratios and 95% CIs for host and microbial factors will be estimated from the models and have a cluster-specific interpretation. We anticipate that 85% of all HH contacts (n=2720) will be exposed to a smear positive PTB case. We estimate 40% (n=1280) of these contacts to have Mtb infection, 25% of whom (n=320) would be recently infected.[2] This would result in 48 active TB cases, assuming a 15% 2-year risk of progression to active disease.[21 22] We expect a background rate of active TB, regardless of Mtb infection, of 0.37% per year yielding an additional 24 cases. Therefore, with 72 incident active TB cases and assuming a 10% loss to follow-up, we will have at least 80% power to detect a twofold increased risk of active TB disease among HH contacts

Table 2 Biorepository established in the CTRIUMPH study

Type of specimen	Cohort	Purpose
Whole blood	Active TB Cohort HH Contact Cohort Control Cohort	Transcriptomics
Plasma	Active TB Cohort HH Contact Cohort Control Cohort	Proteomics, metabolomics, lipidomics and non-cellular measures of immune response (ie, cytokines, chemokines and related reactants)
PBMCs	Active TB Cohort HH Contact Cohort Control Cohort	CD4, CD8, cellular immune responses and other immunological measures of treatment response
Sputum	Active TB Cohort HH Contact Cohort Control Cohort	mRNA, microbiological measures and host immune markers
Mtb isolates	Active TB Cohort HH Contact Cohort	Full genome sequencing for virulence factors
Urine	Active TB Cohort HH Contact Cohort Control Cohort	Metabolomics and measures of microbial markers
Hair	Active TB Cohort HH Contact Cohort Control Cohort	Nicotine exposure and PK studies
QGIT supernatant	HH Contact Cohort Control Cohort	Non-cellular measures of immune response (ie, cytokines, chemokines and related reactants)

HH, household; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetic; QGIT, Quantiferon Gold in Tube.

with a 10% point higher prevalence of key risk factors of DM, HIV, AP exposure, smoking and undernutrition.

Aim-3: To explore host and microbial factors associated with Mtb transmission. The analysis set will be HH members of index PTB cases. The primary outcome of incident Mtb infection will be defined as positive TST or QGIT in children <5 years or seroconversion of TST or QGIT among HH contacts. A multivariate random effects Poisson regression model, adjusted for independent variables measured at the HH level, will be used to estimate the relative risk of Mtb transmission to HH contacts in the presence of host and microbial factors.

Planned substudies

The CTRIUMPH cohort research unit is designed to support highly relevant substudies advancing TB research in the Indian setting. For instance, the Pharmacokinetics (PK) substudy will describe population PK of first-line anti-TB drugs taking into account factors known to affect drug concentrations, such as slow isoniazid metaboliser genotypes that are prevalent in Indian populations,[23] and examining the relationship between drug concentrations and TB treatment outcomes. Plasma samples collected in the CTRIUMPH study will be analysed for NAT2 or SLCO1B1 genotypes and minimum inhibitory concentrations for first-line anti-TB drugs will be determined. Additionally, this substudy will explore the role of novel assays using hair samples for long-term drug exposure assessments. Results from the PK substudy will help identify optimal antituberculosis drug dosage for Indian populations.

Despite microbiological cure, a significant proportion of PTB cases have chronic respiratory impairment.[24] The Lung Health substudy will identify host factors associated with residual respiratory impairment in adult PTB cases. The underlying mechanistic pathways of lung inflammation and remodelling will be explored. Plasma samples collected in the CTRIUMPH study will be analysed for a multiplex of inflammatory biomarkers (MMP-1, MMP-3, MMP-9, IL-4, IL-6, IL-8, IL-10, IL-12, CRP, CC16, TNF-α, INF-γ). The lung health of participants will be characterised by spirometry assessments, 6 min walk testing and standardised respiratory questionnaires. Additionally, this substudy will characterise a participant's exposure to air pollution using personal and home-based PM2.5 and CO monitors. Further, sputum microbiome diversity and its association with respiratory impairment will be explored. Results from the Lung Health substudy will help identify a risk-set of patients with PTB who may benefit from additional monitoring and adjunct host direct immunotherapy aimed at preventing pulmonary morbidity.

The CTRIUMPH study, consisting of well-characterised contacts of PTB cases, is particularly well suited to address knowledge gaps in our understanding of the host immune response to Mtb infection. The Innate Immunology substudy will utilise bio-banked samples from the HH Contact Cohort and describe the role of natural killer cells and mucosal-associated invariant T-cell responses in protecting against Mtb infection. Additionally, we will use flow cytometry and systems biology analytical tools designed for large data sets to measure an array of NK, NK-T and γδ T cell responses to

Table 3 Outcome definitions for the CTRIUMPH study

Cohort	Outcomes	Definition
Active TB Cohort	Treatment failure	*Bacteriological failure*: One or more specimens from the respiratory tract or extrapulmonary site that are culture-positive for Mtb at month-5 or later during treatment; and the culture has not been determined to be false-positive. *Clinical failure*: Persistence, progression or recurrence of signs and symptoms of TB that are determined to be due to TB and not due to another underlying cause.
	Recurrence	*Bacteriological recurrence*: Among participants who did not experience bacteriological or clinical treatment failure, a clinical specimen collected from any anatomical site during the follow-up phase is found to be culture-positive for Mtb; and the culture has not been determined to be false-positive. *Clinical relapse*: Clinical or radiological evidence of TB during the follow-up phase among participants who did not experience bacteriological or clinical treatment failure.
	Death	A participant who dies for any reason after consenting to participate and prior to the end of the study.
	Cure	The participant has two or more consecutive cultures negative for Mtb by the end of the standard first-line multidrug therapy.
HH Contact Cohort	Incident TB disease*	*Definite TB*: Culture confirmation of Mtb from any anatomical site during the follow-up phase. *Probable TB*: Signs and symptoms consistent with TB disease and AFB detected with smear microscopy. Among children <14 years of age in whom AFB microscopy results are negative or not available; CXR consistent with intrathoracic disease, or positive clinical response to standard multidrug ATT, or documented contact with an active case of TB, or immunological evidence of Mtb infection. Possible TB: Signs and symptoms suggestive of TB disease and CXR consistent with intrathoracic disease, or positive clinical response to standard multidrug ATT, or documented contact with an active case of TB, or immunological evidence of Mtb infection.
	Incident TB infection	Seroconversion of TST or QGIT among HH contacts during follow-up, or a positive TST or QGIT at entry in children <5 years of age.
	Mtb infection not detected	HH contacts who are TST and QGIT negative at enrolment and who remain TST and QGIT negative and are not diagnosed with incident TB disease during their follow-up duration.

*Based on international consensus guidelines for TB case definitions 20.
AFB, acid-fast bacilli; ATT, antituberculosis treatment; CXR, chest X-ray; HH, household; QGIT, Quantiferon Gold in Tube; TB, tuberculosis; TST, tuberculin skin test.

ex vivo Mtb antigenic stimulation. Results from this study will help identify immune correlates for Mtb infection, thereby informing future studies aimed at evaluating potential vaccine candidates.

Additional fundamental and translational studies are planned and include the whole blood transcriptome for genomic studies, serial host proteomic bio-signatures and markers of host inflammation and oxidative stress through collaborations with the Institute of Genomics and Integrative Biology (IGIB), Translational Health Science and Technology Institute (THSTI) and Chest Research Foundation (CRF) in India, and the Center for Environmental Health at JHU.

Organisational overview

The CTRIUMPH administrative structure will comprise a Leadership Group (LG), scientific advisory boards (SAB), community advisory boards (CAB) and working groups (WG). The LG will provide operational and scientific oversight. The SAB will consist of experienced Indo-US TB researchers and leaders. The CAB, comprised of community leaders and organisations, will advise the LG on the utility and practicality of proposed studies. The scientific WG, comprised of Indo-US TB researchers with specific scientific expertise, will contribute to intellectual productivity and output in their respective scientific disciplines, while the operational WG, consisting of investigators and staff with specific operational expertise, will oversee the management of day-to-day operations and logistics. Importantly, WGs will ensure cohort performance by standardising the study protocol, data collection instruments and operating procedures across both study sites. Quality control (QC) and quality assurance (QA) measures and accrual and retention monitoring procedures will be established to ensure high quality data.

Additionally, CTRIUMPH is a participating cohort research unit of the Regional Prospective Observational Research in Tuberculosis (RePORT) International Network.[25] RePORT International represents a consortium of regional cohorts in India, Brazil and Indonesia that are linked through the implementation of a common standardised protocol for data and specimen collection, and is poised to address critical research needs in TB. Our study will contribute to a larger network of newly created cohort studies in India (RePORT India) which will greatly facilitate and encourage new scientific collaborations within India as well as new Indo-US and South-South collaborations. Key data elements and stored specimens will be shared between RePORT participating sites fostering greater global clinical research capacity and increased local access to quality data for members of the RePORT network and their domestic and international collaborators.

Ethical considerations

The CTRIUMPH protocol and informed consent forms are approved for scientific content and compliance with human subjects' research regulations by the Institutional Review Boards of NIRT, BJMC and JHU. All investigators and study personnel are trained in research ethics and human subjects' protection.

DISCUSSION

Despite the substantial global progress towards TB control, knowledge gaps persist in our understanding of risk factors responsible for poor TB treatment outcomes. Clinical research necessary for developing effective diagnostic, therapeutic and preventive modalities will greatly benefit from reliable and reproducible surrogate biomarkers predictive of key TB outcomes. The vision of CTRIUMPH is therefore to establish a research platform for clinical and biomarker discovery studies with the potential to address knowledge gaps and inform TB control strategies, both in the Indian setting and globally. Through the CTRIUMPH study, we hope to identify biomarkers and correlates predictive of progression from Mtb infection to active disease which can help identify latently infected individuals who may greatly benefit from targeted preventive therapy. Additionally, we hope to identify biomarkers and correlates, during early clinical care, that are predictive of treatment failure, relapse or cure and can serve as intermediate end points for clinical trials, thereby accelerating clinical research of novel anti-TB drugs and regimens. Furthermore, we hope to identify biomarker and correlate profiles suggestive of emerging drug resistance, which are critically important to inform early management of drug-resistant TB. Finally, we anticipate CTRIUMPH to serve as a successful model for long-term Indo-US scientific collaborations, and as a mechanism to support relevant studies that can leverage regional research priorities and infrastructure.

Prospective data collection is particularly important for TB biomarker discovery. A key strength of the CTRIUMPH study is its ability to serially link high quality clinical and epidemiological data with a strategic bio-repository in a high-burden setting. Furthermore, standardised protocol, data collection and operating procedures will ensure comparable and high quality data across both study sites. Multidisciplinary teams of experts will ensure optimal study oversight. Additionally, we will implement an electronic mHealth-based data-capture system with built-in QC/QA procedures to facilitate optimal data monitoring and quality.[26] Finally, specific goals and objectives of CTRIUMPH notwithstanding, its broad research infrastructure and diverse study population lends itself to future collaborative research opportunities within the scientific framework of the study.

CTRIUMPH is an ambitious study and may therefore be susceptible to threats and challenges arising from its expansive scope of activities. Key among these is likely to be participant fatigue due to a substantial amount of clinical data and specimens being collected at each of the numerous study visits, which may compromise study retention and completeness of data. Additional challenges may include maintaining optimal study logistics, effective study monitoring, ensuring regulatory oversight and navigating national and international administrative policies. We hope to mitigate these challenges by implementing QC/QA tools, periodic study monitoring and evaluation processes, standardising and pre-testing operating procedures, and by ensuring community and bureaucratic stakeholder involvement and support at all stages of the study.

TB is among the oldest known diseases and continues to affect mankind today. The global call to end TB requires bold evidence-based strategies and continued innovation. In the coming few years, we anticipate CTRIUMPH generating high quality evidence to inform local and global TB control strategies, and serving as a platform to advance TB clinical and biomarker discovery research in the 21st century.

Author affiliations
[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[3]National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India
[4]Johns Hopkins Clinical Trials Unit, Byramjee Jeejeebhoy Government Medical College, Pune, Maharashtra, India
[5]Byramjee Jeejeebhoy Government Medical College, Pune, Maharashtra, India
[6]Indian Council of Medical Research, New Delhi, India

Collaborators The CTRIUMPH team listed in alphabetical order—Aarti Kinikar, Akshay Gupte, Alamelu Raja, Amita Gupta, Amita Nagraj, Anand Kumar B, Andrea DeLuca, Anita More, Anju Kagal, Archana Gaikwad, Ashwini Nangude, Balaji S, Beena Thomas, Bency Joseph, Bharath TK, Brindha B, David Dowdy, Deepak Pole, Devanathan A, Devi Sangamithrai M, Dileep Kadam, Divyashri Jain, Dolla CK, Gabriela Smit, Gangadarsharma R, Geetha Ramachandran, Hanumant Chaugule, Hari Koli, Hemanthkumar, Jeeva J, Jessica Elf, Jonathan Golub, Jyoti Chandane, Kanade Savita, Kannan M, Kannan Thiruvengadam, Karthikesh M, Karunakaran S, Kelly Dooley, Lakshmi Murali, Lavanya M, Luke Hanna, Madasamy S, Mageshkumar M, Mangaiyarkarasi S, Mahesh Gujare, Manoharan S, Michel Premkumar M,

Munivardhan P, Murugesan S, Gomathy NS, Nagaraj, Neeta Pradhan, Nikhil Gupte, Nishi Suryavanshi, Chandrasekaran Padmapriyadarsini, Ponnuraja C, Premkumar N, Rahul Lokhande, Rajkumar S, Ranganathan K, Rani S, Renu Bharadwaj, Renu Madewar, Rewa Kohli, Robert Bollinger, Rosemarie Warlick, Rupak Shivakoti, Sahadev Javanjal, Sandhya Khadse, Sathyamurthi P, Shalini Pawar, Shashank Hande, Shital Muley, Shital Sali, Shri Vijay Bala Yogendra Shivakumar, Shubhapriya K, Shyam Biswal, Silambu Chelvi K, Smita Nimkar, Soumya Swaminathan, Sriram Selvaraj, Sundeep Salvi, Sushant Meshram, Swapnil Raskar, Uma Devi, Vandana Kulkarni, Vidula Hulyalkar, Vidya Mave, Vinod Tayawade, Vrinda Bansode, Yogesh Daware.

Contributors AG drafted the first version of this manuscript. AG and SS. conceived and designed the overall study. VM, CP, NG, NS, RK, SVBYS, KT, AD, GR, LEH NP, NSG and AG are responsible for the study oversight, management and co-ordination. All authors reviewed the manuscript for intellectual content and approved the final version of the report.

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