Critical Path to Tuberculosis Drug Regimens: Global Collaboration to Accelerate Development of Novel Drug Regimens and Rapid Drug Susceptibility Tests for Tuberculosis

Article · July 2015
DOI: 10.18063/JMDS.2015.01.006

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REVIEW ARTICLE

Critical Path to Tuberculosis Drug Regimens: Global collaboration to accelerate development of novel drug regimens and rapid drug susceptibility tests for tuberculosis

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Abstract: The Critical Path to Tuberculosis Drug Regimens (CPTR) initiative aims to support the rational deployment of new tuberculosis (TB) therapies by speeding the development and impact of new and markedly improved drug regimens as well as rapid drug susceptibility tests. Co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance in 2010, CPTR is a coalition comprising the world's leading pharmaceutical companies, product development sponsors, diagnostic companies, regulatory agencies, and civil society organizations which support and catalyze advances in regulatory science, the development of infrastructure, and other progress needed to accelerate the pace of development and introduction of novel regimens and rapid drug susceptibility tests. This manuscript summarizes the work of two subgroups within CPTR, the Regulatory Sciences and Rapid Drug Susceptibility Test consortia, and their efforts to drive innovation. These consortia are supported by a robust TB clinical data platform, which continues to evolve through contributions of contemporary TB clinical trial data sets as well as whole genome sequence level data from isolates across the globe. Examples of innovation are described and include a recently-qualified drug development tool and emerging programs to support the development of clinical trial simulation tools.

Keywords: tuberculosis, TB drug regimens, TB diagnostics, clinical trial simulation tools, consortium

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Received: April 30, 2015; **Accepted:** May 13, 2015; **Published Online:** July 7, 2015

Citation: Hanna D, Schito M and Romero K, 2015, Critical Path to Tuberculosis Drug Regimens: Global collaboration to accelerate development of novel drug regimens and rapid drug susceptibility tests for tuberculosis. *Journal of Medicines Development Sciences*, vol.1(1): 51–58. http://dx.doi.org/10.18063/JMDS.2015.01.006.

1. The Need for Novel, Safer and Faster-acting TB Drug Regimens and Rapid Drug Susceptibility Tests for Tuberculosis

As of 2015, tuberculosis (TB) remains the world's single most deadly infectious disease impacting one-third of the population. TB claims 1.5 million lives annually, despite the fact that therapies have been available for more than four decades[1]. Current standard of care treatment paradigms face major challenges due to (1) long duration of treatment (9 months to 2 years depending on susceptibility profiles); (2) serious adverse drug reactions (magnified with concomitant therapies for HIV); and (3) the emergence of drug resistance. Despite the availability of therapies, patient treatment is frequently not optimized due to the difficulty in determining if the mycobacteria are susceptible to the four-drug cocktail that was prescribed. Therefore, rapid drug susceptibility tests (RDSTs) are required to improve the management of TB patients, support the rational use of new TB drug regimens, and increase under-

standing of the global burden of drug-resistant TB. Despite the need to optimize TB therapy and susceptibility testing, drug and diagnostic innovation has been stagnant for many decades, driven largely by the low return on investment and the existence of therapies that were deemed sufficient. This stagnation was unacceptable to many in the global health community bringing about a tidal shift in thinking. As a result, a few existing antibiotic classes (such as nitroimidazoles and oxazolidinones) have emerged with the potential to serve as new and more effective combination partners for the treatment of TB.

2. The Opportunity for Global Collaborative Partnership

An evaluation of the TB drug development landscape, regulatory environment and global implementation plan highlighted key areas where innovation would be required to successfully advance entirely new drug regimens in an efficient manner. A novel regimen is critical for many reasons including the need for decreased drug–drug interactions, optimization of dosing of individual components and shorter treatment duration to increase patient compliance compared to current standard of care. Additionally, an optimized standard treatment approach can be linked with standardized testing for TB. First and foremost, optimized paradigms for early clinical testing of novel combination regimens and supporting regulatory strategies would be critical.

In 2010, the CPTR consortium[2] was launched to address these key gaps in innovation, acknowledging the need for a cross-sector collaborative approach. This global partnership, led by the Bill & Melinda Gates Foundation, TB Alliance and the Critical Path Institute, was initially designed to accelerate novel TB drug regimen development as well as global regulatory processes to support speed to innovation. Founding partners include representatives from the pharmaceutical sector (Janssen, Pfizer, AstraZeneca, Sequella, Otsuka), the government sector (US Centers for Disease Control, US National Institutes Allergy and Infectious Diseases) the non-profit sector (TB Alliance), patient advocacy groups (Treatment Action Group), the World Health Organization (WHO), the academic sector, and Regulatory Health Authorities (European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The operational design of the consortium is intended to drive key areas of innovation addressed through working groups consisting of subject matter experts representing each sector and stakeholder group (Figure 1).

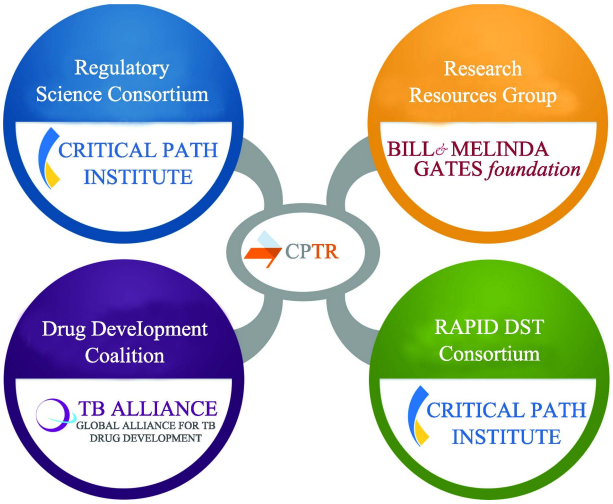

Figure 1. CPTR working group model.

For purposes of this manuscript, we will focus on the efforts of the Regulatory Sciences and Rapid Drug Susceptibility Testing consortia within CPTR, given their emphasis on scientific and regulatory innovation. Other CPTR consortia which will not be discussed here include the Research Resources Consortium, which is keenly focused on critical parallel issues such as TB Clinical Trial Infrastructure and the Access and Appropriate Use and Community Engagement efforts.

3. The CPTR Regulatory Sciences Consortium

3.1 Decreasing Risk and Increasing Confidence in TB Drug Regimen Development

The working group projects led by the CPTR Regulatory Sciences Programs are focused on de-risking critical decision points as part of the TB regimen development process. These efforts include the validation of new drug development tools, increasing confidence in biomarkers for TB, and the development of TB clinical trial modeling tools for better trial design through simulation. Each of these programs is enabled by the CPTR TB clinical trial data platform that includes critical data contributions by, among others, Janssen, CDC, and the TB Alliance. These contemporary clinical trial data sets have been mapped to the Clinical Data Interchange Standards Consortium (CDISC) TB Data Standard[3], allowing the data to be aggregated for more informed statistical analysis. The TB data standard was developed as part of the CPTR Regulatory Sciences team efforts in partnership with CDISC. This data standard was a fundamental enabler

to the data aggregation required to develop our innovative drug development tools and achieve modeling and simulation goals. Several of the programs driven by the CPTR regulatory sciences project teams are summarized below.

3.2 The *in vitro* Hollow Fiber Model System for Tuberculosis (HFS-TB) as a Translational Model Between Pre-clinical and Early Clinical Drug Development Stage Gates

Anti-TB drug regimen development strategies will be greatly enhanced using validated, reliable pre-clinical data that support the informed selection of each new entity to be tested in early combination studies. Beyond compound selection, quantitative pharmacokinetic and pharmacodynamic (PK/PD) information is needed to support informed dose selection for those early clinical combination regimens. In addition, non-clinical novel methodologies and drug development tools (DDTs) with demonstrated predictive accuracy for clinical and microbial outcomes are needed to support effective drug development decision-making. Endorsement of these DDTs by regulatory authorities is critical for drug developers as it promotes confidence in their use and supports incorporation of data generated by these DTTs in Investigational New Drug (IND)/Clinical Trial Authorization (CTA) and Marketing Authorization Application (MAA)/New Drug Application (NDA) filings. The *in vitro* hollow fiber system of tuberculosis (HFS-TB) is a DDT that can support these needs by providing a quantitative PK/PD understanding of new TB drugs and regimens. These data used in partnership with other preclinical data can support and expedite selection of more optimized regimens.

The HFS-TB is able to recapitulate concentration–time profiles (exposure) observed in patients for a single drug, as well as for multiple drugs tested in combination. The HFS-TB model (Figure 2) consists of a peripheral or pharmacodynamic compartment for the *Mycobacterium tuberculosis* inoculum and a central drug-containing or pharmacokinetic compartment. The hollow fibers are semipermeable fiber bundles with pores of different molecular-weight cutoffs that are encased in a plastic cartridge. Drugs are administered to the central compartment via a syringe pump which is programmed to mimic desired peak concentration and time to peak concentration encountered in patients. The drug(s) diffuse across the hollow fibers into and out of the peripheral compartment via first-order kinetic principles. The HFS-TB can be used to

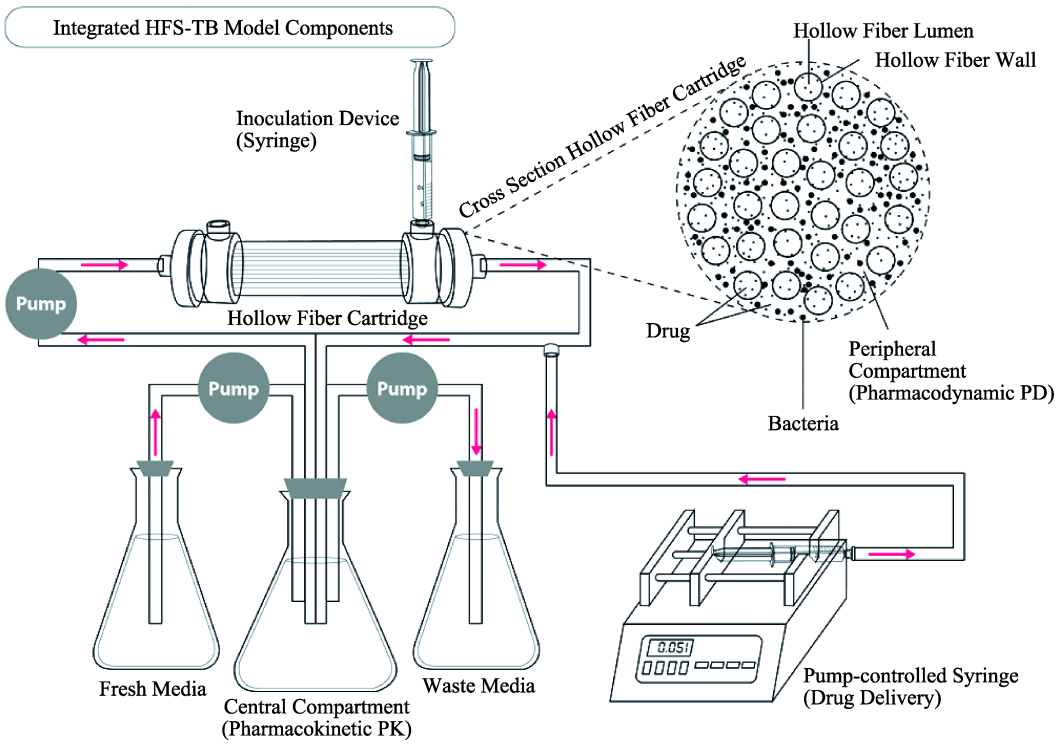

Figure 2. *In vitro* HFS-TB model.

mimic a single drug profile or combination drug profile in the central compartment with a half-life that mimics that encountered in lungs of patients. *Mycobacterium tuberculosis* cells are too big to pass into the central compartment and thus are confined to the peripheral compartment.

The HFS-TB supports the evaluation of such drug exposures for the ability to kill *M. tuberculosis* in a variety of physiological conditions. This quantitative output can be used to inform the selection of optimal drug exposures, drug doses, susceptibility breakpoints, and optimal combination regimens in patients, and to inform the design of nonclinical experiments in animal models, based on Monte Carlo simulations.

The Pre-Clinical and Clinical Sciences Working Group within CPTR executed an evidence-based evaluation of the predictive accuracy of the HFS-TB to validate this model as a novel DDT. This extensive effort was enabled through the collaborative efforts of subject matter experts representing the pharmaceutical industry, academia, product development partnerships, and regulatory authorities including the FDA and the EMA. This team developed a comprehensive analysis plan following the regulatory guidance documents for novel methodology/DDT qualification and engaged in discussions with the FDA and the EMA.

In order to pursue regulatory endorsement for the HFS-TB as a DDT, the results from the quantitative predictive accuracy analyses were submitted to both the FDA and EMA. The findings were presented to the FDA via the voluntary exploratory data submission mechanism. The findings were also presented to the EMA via the qualification advice mechanism through EMA's Scientific Advice Working Party (SAWP) which led to a qualification opinion mechanism by EMA's Committee for Medicinal Products for Human Use (CHMP). EMA issued a qualification opinion for the HFS-TB[4] and the FDA has described its utility as part of the updated guidance on TB drug development. Qualification and other mechanisms of regulatory assessment for new DDTs and biomarkers increase the pharmaceutical industry's confidence in implementation of the tools and biomarkers as part of the drug development process for new drugs. In addition, the decreased review times when qualified tools or biomarkers are used as part of their supporting data for new INDs and CTAs, provide tangible benefits for drug developers (Figure 3).

Clinical trials for new tuberculosis drugs and drug regimens are long in duration and very costly. There are several opportunities to increase confidence in the transition between key development phases by improving understanding of the PK/PD relationships and translation as well as developing robust clinical trial simulation tools that can improve the design of clinical trials. CPTR has undertaken a number of collaborative projects to increase confidence in the tuberculosis drug development process as noted in Figure 4.

3.3 Physiologically-Based Pharmacokinetic (PBPK) Model for Evaluating Systemic Drug Distribution in the *Mycobacterium Tuberculosis*-Infected Lung

There is a need to better understand the distribution of anti-TB therapeutics into lung tissue and lung lesions caused by this disease. PBPK modeling captures the complex mechanistic drug distribution processes in the infected, inflamed, and damaged lung with the goal of improving treatment and regimen selection designed to optimize drug exposures across the heterogeneous sites of action in the lung[5]. Accordingly, the CPTR modeling and simulation workgroup, part of the Regulatory Sciences Consortium, partnered with SimCyp to develop a PBPK model describing the TB-infected lung in a virtual South African population. This model is based on compound files for standard-

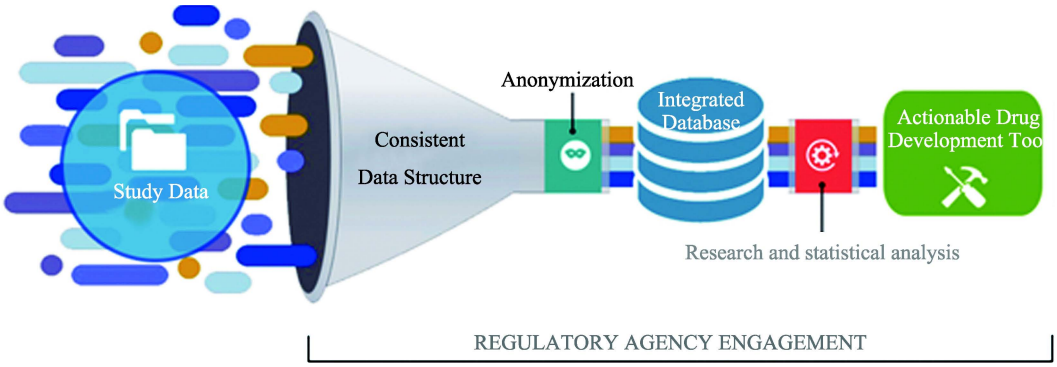

Figure 3. Drug development tool evaluation process.

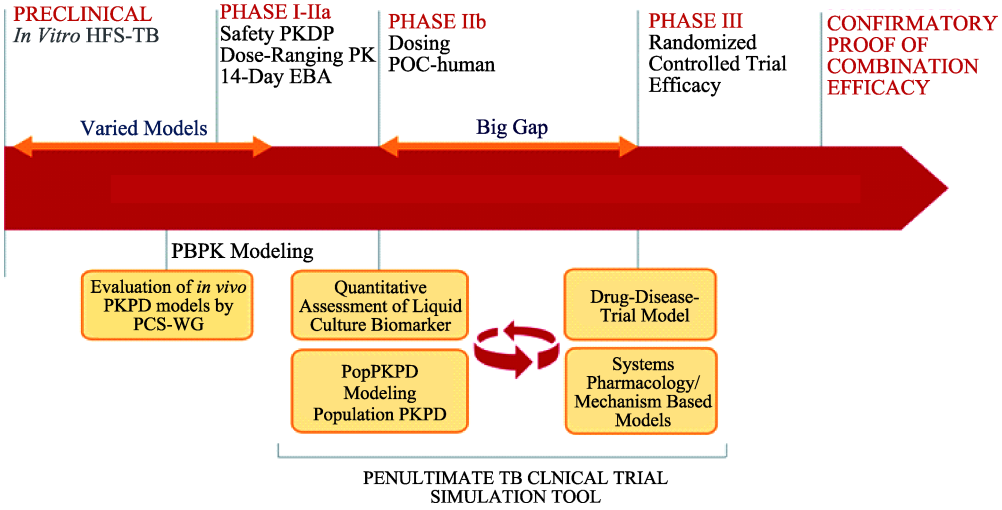

Figure 4. Opportunities to improve tuberculosis drug development paradigm.

of-care drugs and is implemented on the SimCyp platform. This team is working on refinements to the model, which will include sub-compartments that describe drug penetration into granulomas, and compound files for newer anti-TB drugs.

3.4 Population Pharmacokinetic and Pharmacodynamic (PK/PD) Model Derived From Therapeutic Monitoring Data

A significant challenge to developing better clinical trial simulation tools for TB is the lack of clinical trial data, especially trials that include PK/PD assessments[6–8]. Therefore, the CPTR Regulatory Sciences Consortium is spearheading an effort with our University of Florida partner, which will utilize PK/PD data where therapeutic drug monitoring was practiced. This work will help determine if dose adjustments of anti-TB therapy resulted in different outcomes for each of the first- and second-line TB drugs, along with relevant patient data (covariates). This will allow the exploration of relationships between PK estimates and clinical outcomes of both efficacy and toxicity stratified by the regimens used (particularly for multi-drug resistant (MDR) TB). The results from this effort will be compared to and contrasted with existing guidelines for similar clinical scenarios.

3.5 Evaluation of the Liquid Culture Biomarker to Inform the Development of Tuberculosis Modeling and Simulation Tools

There is a need for quantitative tools to more accurately evaluate efficacy in Phase II clinical trials for combination TB regimens and to more reliably predict clinically relevant endpoints for Phase III clinical trials, based on early efficacy evaluations during Phase II[9,10]. To meet this goal, the CPTR Regulatory Sciences Consortium, in collaboration with our Pharsight partner, will assess the longitudinal changes in time to positivity (TTP) and its relevant sources of variability as a continuous measure in TB patients. In addition, a quantitative model linking changes in TTP from liquid culture to durable cure will be developed[11]. Simulations of longitudinal TTP data will be performed in sub-populations of interest and the resulting effect on durable cure will be determined.

3.6 Mechanism-Based Systems Pharmacology Model for Tuberculosis

New TB drugs and therapy combinations require lengthy, expensive clinical trials. Traditional *in vitro* or *in vivo* murine models are rarely able to represent unique aspects of TB disease and pathology, such as granuloma formation, bacterial resistance, patient non-adherence, or comorbid diseases[12]. Therefore, the CPTR Regulatory Sciences Consortium is developing a novel systems pharmacology model in order to establish a TB simulation (TB sim) framework incorporating mechanism of action for multiple anti-TB agents, pharmacokinetic and bactericidal properties of drugs, drug dosing and duration, granuloma dynamics, risk of bacterial resistance, immune response, and clinically relevant outcomes at a population level. Model parameters will be based on relevant *in vitro* and *in vivo* animal experiments, data emerging from multiple CPTR workgroups, emerging clinical trial results, ongoing systems biology efforts, and biomarker work. As the simulation model framework matures, the goal is to establish predictive metrics of *in vitro* and *in vivo* animal models and emerging bio-

markers for TB. The TB sim model will also be used to explore enhanced clinical trial designs which could shorten clinical development time, and for assessment of specific patient populations.

3.7 QT Risk Assessment and Interpretation in TB Drug Development

QT prolongation has been observed with many of the drugs used to treat TB. However, the clinical risk/benefit and differentiation between TB combination regimens with respect to QT prolongation is unclear[13,14]. This project, led by the CPTR Regulatory Sciences Consortium, in collaboration with Pharsight, aims to (1) collate historical data with TB drugs alone and in combination pertaining to QT effects and associated clinical outcomes (e.g., Torsade de pointes, sudden death, hospitalization) and (2) provide guidance/recommendations on suitable experimental designs (*in vitro*, preclinical, and clinical), data analytical approaches, signal interpretation, and go/no go decision criteria related to QT prolongation in the context of new TB drug combination development.

4. The CPTR Rapid Drug Susceptibility Testing Consortium

4.1 The Need for RDSTs for Tuberculosis

RDSTs are needed to improve the management of TB patients, to facilitate drug development and rational use of new TB drug regimens, and to better understand the global burden of drug-resistant TB. The field has recognized the need for a data-sharing platform that provides a one-stop data source for clinically relevant genotypic and phenotypic information on MTB. Having such data reviewed and validated, and made accessible in one place, would support the development of new RDSTs that can quickly inform appropriate therapy for TB patients. A comprehensive, curated, and easy-to-use data platform of this scope does not currently exist and is a major barrier to the understanding of the relationship between genetic mutations and drug resistance in MTB. This barrier impacts drug and diagnostic developers, clinicians prescribing therapy, and ultimately patients who should have earlier access to appropriate drug regimens. Successful execution of such an extensive database platform requires substantial collaboration from scientists investigating the genetic basis for drug resistance worldwide, and from developers with expertise in database design and implementation ensuring quality and security, while providing assurance that all relevant legal, patient data privacy, and intellectual property standards are met. The CPTR Rapid Drug Susceptibility Testing Consortium can provide the means to accomplish this goal.

4.2 The Opportunity to Leverage the CPTR Collaboration to Ensure Rational Implementation and Deployment of New Tuberculosis Drug Regimens Through Development of Rapid Drug Susceptibility Tests

With two new drugs recently receiving conditional approval (bedaquiline and delamanid), the off-label use of drugs in TB treatment regimens (linezolid and clofazamine), and drugs being used in TB treatment regimens despite having no TB label claims, clinical trials are underway to test new combinations of these and other existing drugs that may prove to be safer and more effective, and allow for shorter treatment duration. If these new treatment regimens prove to be superior to the standard of care, they will be widely adopted by global public healthcare programs and will require improved and novel RDSTs in order to effectively implement them. In addition, the inclusion of new drugs could potentially unify treatment for patients with drug-susceptible infections, as well as for an increasing number of patients who are infected with drug-resistant strains of MTB, or who develop drug resistance during therapy. However, treatment without identifying drug susceptibility runs the risk of employing suboptimal drug regimens with fewer effective drugs. As a small number of TB isolates may be naturally resistant, these new drug regimens may exert selection pressure that could favor the survival and transmission of drug-resistant strains. Therefore, vigilance is required to quickly identify patients who harbor drug-resistant TB, map the trajectory of drug resistance in the population, and develop alternatives to ensure the new drug armaments remain effective.

4.3 Evolution of the Relational Sequencing Data Platform (ReSeqTB) Project

Currently, the correlation between MTB genotypic data and TB drug resistance is widely dispersed among multiple MTB sequence databases, both private and public. Meta-analysis of these divergent published data sets has highlighted gaps and discrepancies in our knowledge, as well as bias that may be present because geographic strain diversity is not well represented. These findings highlight the need for a universally harmonized database platform that is widely accessible and user friendly. With sufficient numbers of globally-derived MTB whole genome sequences, such a statistically powered database plat-

form could robustly facilitate the clinical interpretation of different genetic polymorphisms. Test developers could then rely on such clinically validated genome sequence interpretations and confidently accelerate development of RDSTs for both current and newly emerging TB drugs and drug regimens. To get there, however, thousands of genomic sequences subject to robust quality checks will need to be sourced from multiple global researchers to account for strain variation. In addition, data sets will need to be curated to provide the highest possible confidence in clinical interpretation to support assessment and informed decision making. To accomplish this, CPTR and the Foundation for Innovative New Diagnostics (FIND) secured funding from the Bill & Melinda Gates Foundation and have partnered with the New Diagnostics Working Group, WHO, Centers for Disease Control (CDC), and the National Institute of Allergy and Infectious Disease (NIAID) to develop a platform that supports evidence-based assessment of drug mutations in MTB for diagnostic, research and eventually clinical application. The ReSeqTB database platform, currently in development by CPTR, will serve as a single globally-harmonized repository for the compilation, curation, and validation of existing and newly created data on TB drug resistance correlations (Figure 5).

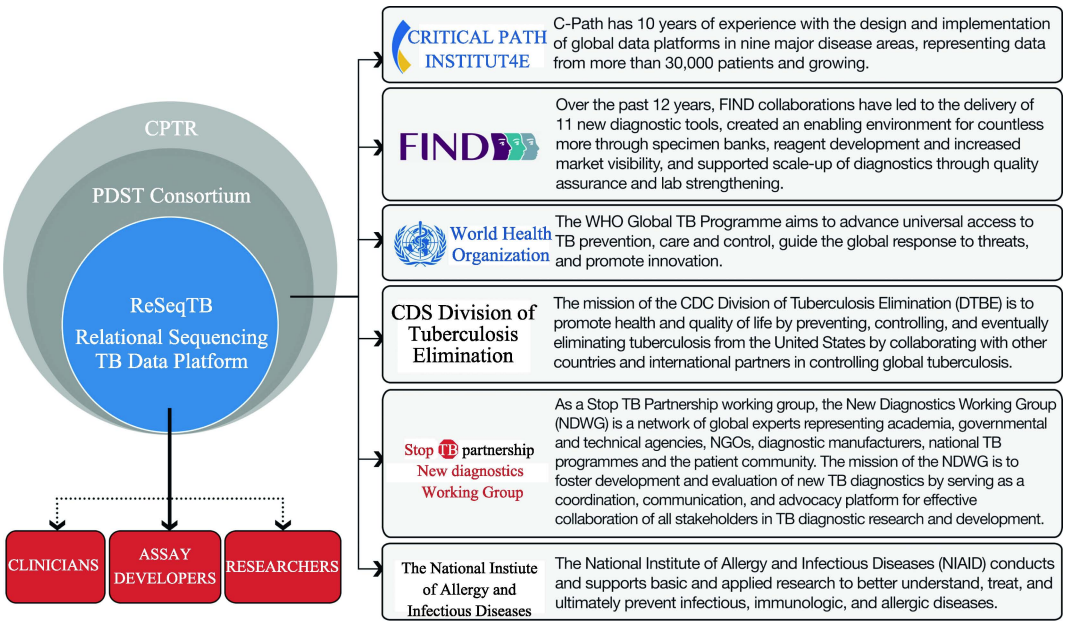

Figure 5. ReSeqTB collaborative partnership.

5. Conclusion

Novel TB drug regimens which are safer and more efficacious and have a shorter duration of treatment than the current standard of care are critically needed. Just as important is the need for accompanying RDSTs to support their usage and protect the durability of new drugs and regimens. Regulatory and scientific innovations supporting these endeavors represent cross-sector collaboration and the secure sharing of data and information sufficient to validate the implementation of new drug development tools as well as the evidence-based development of useful modeling and simulation tools to refine the design of TB clinical trials, key stage gates and modernize the approach to regimen development. Additionally, aggregated data representative of global clinical experience support the evidence-based development of novel assays for TB RDSTs. The CPTR consortium represents a successful partnership model that continues to produce meaningful outcomes that will be made publicly available for use and implementation.

Conflict of Interest and Funding

The authors declare there is no funding or conflict of interest associated with this work. The Critical Path to TB Drug Regimens Initiative is funded by the Bill & Melinda Gates Foundation.

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