

CRITICAL PATH TO TB DRUG REGIMENS INITIATIVE

WORK SCOPE



VERSION 1.0

CRITICAL PATH TO TB DRUG REGIMENS INITIATIVE

OVERVIEW	1
THE BILL & MELINDA GATES FOUNDATION	1
CRITICAL PATH INSTITUTE.....	2
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT	2
CRITICAL PATH TO TB DRUG REGIMENS INITIATIVE	3
STATEMENT OF PRINCIPLES.....	4
STRUCTURE AND GOVERNANCE.....	6
ETHICAL, SOCIAL, AND CULTURAL CONSIDERATIONS	8
CPTR REGULATORY SCIENCE CONSORTIUM	9
CPTR RESEARCH RESOURCES GROUP	12
CPTR DRUGS COALITION.....	12
PROJECT MANAGEMENT AND COMMUNICATIONS	13
PROJECT MANAGEMENT AND ADMINISTRATION	13
EXTERNAL RELATIONSHIPS AND COMMUNICATIONS	13
CPTR REGULATORY SCIENCE CONSORTIUM	14
MISSION & GOALS.....	14
CPTR REGULATORY SCIENCE CONSORTIUM WORKGROUPS.....	14
WORKGROUP 1: INTEGRATED SCIENCES TEAM	15
WORKGROUP 2: DATA STANDARDS AND INTEGRATION	17
WORKGROUP 3: BIOMARKERS AND CLINICAL ENDPOINTS	18
WORKGROUP 4: PRECLINICAL AND CLINICAL SCIENCES	20
WORKGROUP 5: CLINICAL DISEASE PROGRESSION MODELING	22
WORKGROUP 6: HEALTH AUTHORITY SUBMISSIONS	23
INITIAL PROJECT TIMELINE	24
CPTR DRUGS COALITION	24
CPTR RESEARCH RESOURCES GROUP	25
MISSION & GOALS.....	25
CPTR RESEARCH RESOURCES WORKGROUPS.....	26
WORKGROUP 1: CLINICAL TRIALS INFRASTRUCTURE.....	26
WORKGROUP 2: RESOURCE MOBILIZATION	26
WORKGROUP 3: GLOBAL REGULATORY PATHWAYS.....	27
WORKGROUP 4: STAKEHOLDER AND COMMUNITY ENGAGEMENT	27
WORKGROUP 5: ACCESS AND APPROPRIATE USE OF NEW DRUGS.....	27
INITIAL PROJECT TIMELINE	28

OVERVIEW

The Critical Path to Drug TB Regimens (CPTR) Initiative is a broad collaboration of industry, civil society, government, and regulatory officials working together to develop regulatory science that can be used to identify new testing methods for qualification (“tools”) in a specific context of use in the development of promising tuberculosis (TB) drug candidate combinations. CPTR was formally launched on March 18, 2010, at an event in Washington, D.C., with a keynote address by U.S. Food and Drug Administration (FDA) Commissioner Margaret Hamburg.

Current regulatory guidelines allow for development and approval of combination regimens, provided that the contribution of each drug in the regimen can be identified (Figure 1). The CPTR Initiative will work with industry, academic, non-profit, government and regulatory scientists to identify tools and methods that establish the value of each candidate drug in a new TB regimen, so that these drugs can be tested together to allow the acceleration of the development and review of new TB combinations.

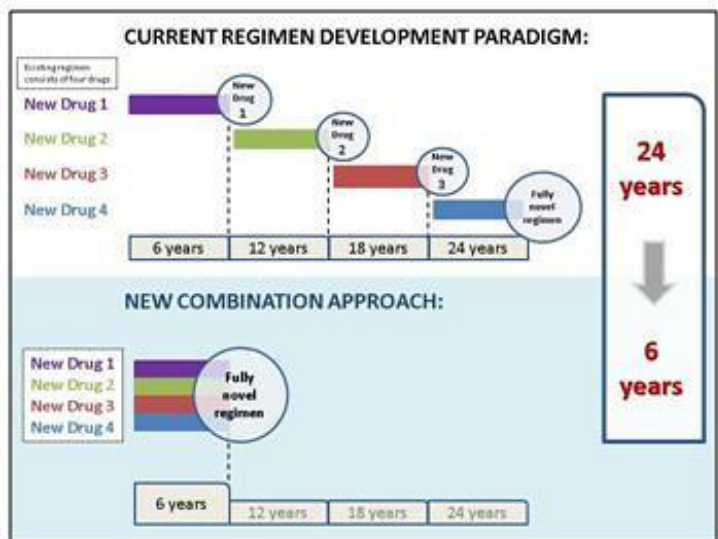


Figure 1: A New Regimen Development Paradigm

The Critical Path Initiative, which was launched by the FDA in 2004 and later authorized in the FDA Amendments Act, is FDA's program to modernize the scientific methods and processes used to transform a potential human drug, biological product, or medical device from a discovery or "proof of concept" into a medical product. This effort focuses on developing regulatory science which defines improved testing methods and processes to evaluate the safety and effectiveness of new medical products. The CPTR Initiative will work closely with regulatory scientists at the FDA and European Medicines Agency (EMA) to further the mission of the Critical Path Initiative.

CPTR was developed and is managed by a partnership of the Bill & Melinda Gates Foundation (Foundation), Critical Path Institute (C-Path), and the Global Alliance for TB Drug Development (TB Alliance).

THE BILL & MELINDA GATES FOUNDATION

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation (Foundation) works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people—especially those with the fewest resources—have access to the opportunities they need to succeed in school and life. Based in Seattle, Washington, the

Foundation is led by CEO Jeff Raikes and Co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.

The Foundation's Global Health Program harnesses advances in science and technology to save lives in poor countries. The Foundation focuses on the health problems that have a major impact in developing countries but that get too little attention and funding. Where proven tools exist, the Foundation supports sustainable ways to improve their delivery. Where they do not, it invests in research and development of new interventions, such as vaccines, drugs, and diagnostics. Their work in infectious diseases focuses on developing ways to fight and prevent enteric and diarrheal diseases, HIV/AIDS, malaria, pneumonia, TB, and neglected and other infectious diseases.

CRITICAL PATH INSTITUTE

Critical Path Institute (C-Path) is an independent non-profit organization that operates under a Memorandum of Understanding with the FDA to support its Critical Path Initiative on developing improved testing methods for new medical products. C-Path has been successful in advancing the drug development process by creating and managing collaborations that allow highly competitive companies and regulatory agencies to work together and share precompetitive data and knowledge. C-Path's approach has been to:

- Form collaborations based on an effective legal agreement that enables rapid and broad open sharing of scientific data and knowledge by all parties;
- Develop a process that results in scientific consensus among scientists from industry, regulatory and other government agencies, and academia, for preferred testing methods for new drugs, diagnostics, and devices; and
- Obtain regulatory qualification of innovative testing methods.

C-Path's collective consortia include over 600 participating scientists from 29 pharmaceutical and biotechnology companies, seven patient advocacy organizations, academic advisors and representatives from regulatory agencies including the FDA, European Medicines Agency (EMA), and the National Institutes of Health (NIH).

These consortia employ novel scientific approaches that incorporate advanced methods in medical product development and bring innovation to drug development by contributing to the science base in support of regulatory review and decision making. For example, C-Path's Predictive Safety Testing Consortium received the designation of "qualification" by the FDA, EMA, and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for seven new biomarkers for specific uses in testing the renal safety of new drugs in clinical development. The "critical path" process has the proven ability to deliver methods that can improve drug development. That process is now well-defined and available for other important public health challenges such as TB.

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

The Global Alliance for TB Drug Development (TB Alliance) is a product development partnership working to develop new, simpler, shorter TB treatments. The TB Alliance combines the research and development expertise of its own staff with the skills and resources of its partners to streamline and

accelerate TB drug development. The organization manages the largest portfolio of TB drug research and development projects in history, with more than 20 projects and three compounds in clinical development.

Since its founding in 2000, the TB Alliance has been a catalyst in the field of TB drug development and has built collaborations with a range of public and private partners, including pharmaceutical and biotechnology companies and academic institutions, from around the world. As part of its not-for-profit mandate, any TB treatments resulting from these partnerships must be available and affordable to those most in need.

CRITICAL PATH TO TB DRUG REGIMENS INITIATIVE

Fortunately, there is now significant momentum in global efforts to fight TB. This is largely due to commitments by governments throughout the world, increased funding from philanthropic organizations, new industry efforts, novel platforms for sharing knowledge, the rise of product development partnerships, and an overall increased attention to global health. Also at this time, a significant number of promising TB drug candidates, vaccines, and diagnostic tests are in pre-clinical or clinical development. This lays the foundation for the unprecedented opportunity for a truly innovative approach.

The CPTR Initiative was created to accelerate the development of new TB regimens by catalyzing innovative testing methods, product development partnerships, and novel development strategies. The CPTR Initiative is managed by the Bill and Melinda Gates Foundation, C-Path, and the TB Alliance. Within the CPTR Initiative are three distinct components or “arms:” the CPTR Regulatory Science Consortium, CPTR Drugs Coalition, and CPTR Research Resources Group. While each arm has a unique purpose, they also support the function and work of the others. In fact, there may be considerable collaboration across workgroups and arms (Figure 2).

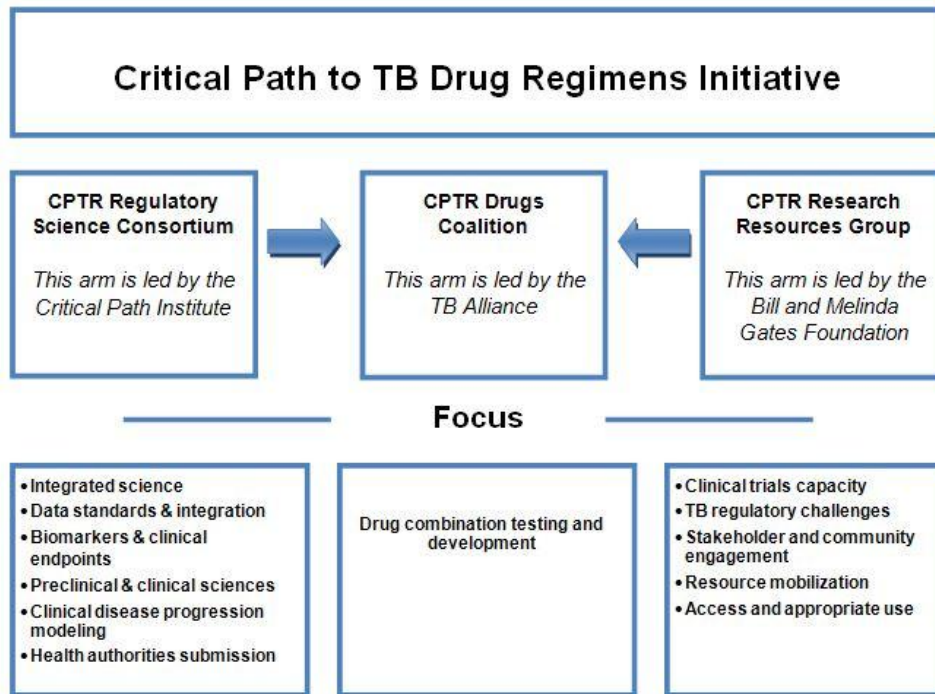


Figure 2: CPTR Initiative Organization, Structure and Function

STATEMENT OF PRINCIPLES

The CPTR Initiative is a broad collaboration of pharmaceutical companies; government, regulatory, and multilateral agencies; donors; academia; advocates; and non-government organizations that aim to accelerate the development of new, safe, and highly effective TB treatment regimens with shorter therapy durations. Its mission is to address an urgent public health need—with the goal of saving millions of lives.

TB AND DRUG-RESISTANT TB ARE MAJOR THREATS TO GLOBAL HEALTH

Although it is often thought of as a disease of the past, 1.7 million people die from TB every year. One-third of the world’s population is infected with the TB bacterium and approximately 9.8 million people develop active disease annually. The rise of drug-resistant TB and TB co-infection with HIV has further exacerbated the global epidemic. Strains of TB that are resistant to all major anti-TB drugs have emerged and can be found in every country. In 2007, there were more than 500,000 cases of multidrug-resistant and extensively drug-resistant TB. Unless these trends are reversed, drug resistance raises the specter of future, untreatable TB epidemics.

NEW TB REGIMENS ARE URGENTLY NEEDED

Today’s TB drugs are more than 40 years old. The commonly used regimens for drug-susceptible TB are unacceptably long, and treating drug-resistant TB can require 24-30 months of prolonged therapy, plagued by significant side effects. These drawbacks decrease patient compliance, which significantly contributes to the rise of further drug resistance. Safer and more effective TB regimens could sharply reduce the duration of treatment for drug-susceptible and drug-resistant TB. However, given the

resilient nature of the bacterium and shortcomings in today's antibiotics, improved TB treatment will likely require a combination of effective antibiotics that includes more than one new drug.

NEW, INNOVATIVE MODELS ARE NEEDED FOR TB REGIMENS DEVELOPMENT

Standard drug development has traditionally required that each new drug be evaluated and approved separately before it is tested in combination with other new compounds. Using this approach, obtaining regulatory approval for a new three- or four-drug combination TB therapy could take more than 20 years. With 5,000 people dying of TB each day, and drug resistance continuing to spread, 20 years is far too long to wait.

UNPRECEDENTED OPPORTUNITY TO WORK TOGETHER TO OVERCOME THESE CHALLENGES

Today, a significant number of promising TB drug candidates are in pre-clinical or clinical development. Simultaneously, there is new momentum in global efforts to fight TB, owed largely to government investments in research and clinical trial capacity, increased philanthropic funding, industry commitments, the rise of product development partnerships, and overall increased attention to global health. Now is the time for a new, innovative approach: develop the regulatory science and infrastructure needed to collaboratively test TB drug candidates in combination early in their development.

All participating parties commit to work together to accelerate the development of new TB drug regimens and agree to:

- Develop a statement of guiding principles and/or policy concerning information sharing and collaboration among international organizations, industry, and regulatory agencies to innovate and accelerate TB regimens development and get important new therapies to patients.
- Promote the development of new regulatory approaches that support innovative research into TB therapeutics, evaluate new TB drug combinations safely and effectively, and reinforce current guidelines for development of effective drug combinations.
- Work together, using industry best practices, to test TB drug candidates in combination regimens beginning early in the development process.
- Create a collaborative coordinating structure to oversee this Initiative.
- Explore creative new funding streams for developing novel combination TB therapies.
- Advance efforts to utilize existing clinical trial sites for TB while also building clinical trial site capacity for late-stage combination TB drug trials.
- Support relevant organizations and stakeholders in accelerating procurement of and access to new TB therapies for patients in need.

Accelerated development of new TB regimens is complex and will require taking acceptable, scientifically based risks balanced with careful ongoing scrutiny. Success will require commitments to work together to ensure that effective TB combination therapies are available in the shortest time possible to those who need them most. If successful, this initiative could serve as a model for future collaborative efforts to develop combination therapies for other diseases.

STRUCTURE AND GOVERNANCE

OVERVIEW

The CPTR Initiative's basic structure is built around its three arms: Regulatory Science Consortium, Drugs Development Coalition, and Research Resources Group. Tying the three operating arms together is an eight-member CPTR Initiative Coordinating Group (Figures 3 and 4):

- Two representatives from each of the three arms (one from each Sponsor Organization and one elected by each arm)
- One representative from the Advisory Panel
- One ethics representative

In addition to directing the overall CPTR policy coordinating activities across the three arms, the CPTR Initiative Coordinating Group will consider potential ethical, social, and cultural (ESC) challenges with the guidance of subject matter experts. Examples of issues for consideration include those around the sharing and use of biological specimens and information, clinical research in special populations (e.g., children and women of reproductive age), access to and appropriate use of experimental regimens, and ethical underpinnings of effective community engagement. Section 1.7 details how ESC challenges will be addressed within the CPTR Initiative.

The Advisory Panel will include select experts who will provide guidance to the CPTR Initiative Coordinating Group at the policy and strategic level. It is expected that the Panel will include up to nine members and will meet at least annually.

GOVERNANCE AND LEADERSHIP

While the three operating arms may tailor their specific structures to suit their missions, they will generally work through a series of Workgroups under the guidance of the arm's Coordinating Committee.

Each arm will determine its membership criteria and operating procedures, and it is expected that each Workgroup will elect a chair, and may also select a co-chair, who would participate in the arm's membership body. Each arm would determine the structure, membership criteria, leadership, and operating policies for its Coordinating Committee, which would serve as its governing body. The three arms will coordinate their work through the Initiative Coordinating Group and directly among the arms' Workgroups.

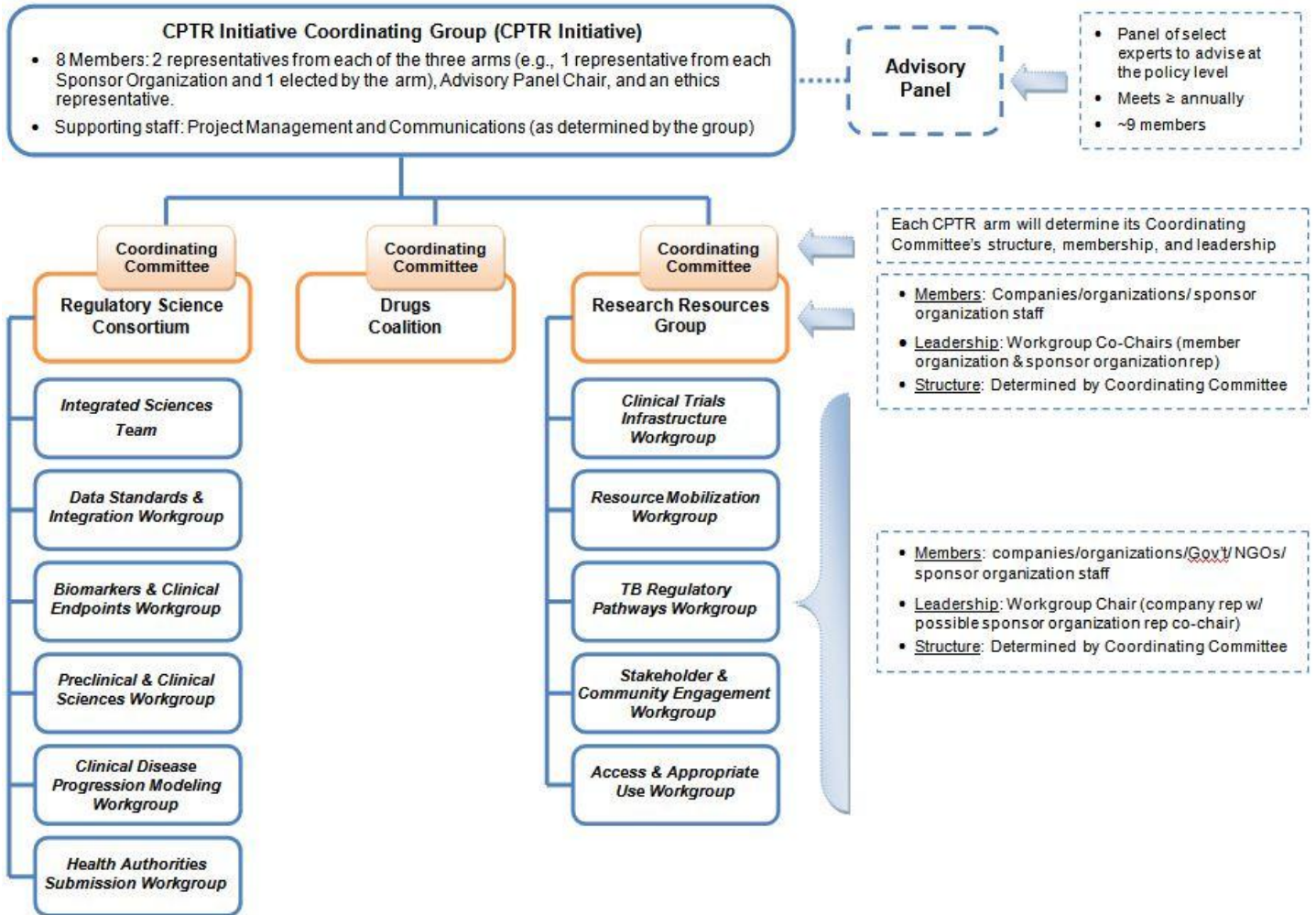



Figure 3: CPTR Governance and Leadership



Group	Key Roles	Examples
CPTR Initiative Coordinating Group	<ul style="list-style-type: none"> Overall CPTR policy, communications, project management, and finances Coordinate among the CPTR arms Disseminate information to and receive input from the Advisory Panel 	<ul style="list-style-type: none"> Provide input to the three arms on the direction and nature of their work, proposed work products, tools, and regulatory submissions Ensure effective project management for the initiative
Advisory Panel	<ul style="list-style-type: none"> Provides a range of experience and perspectives to the CPTR Initiative Coordinating Group on its goals and objectives. 	<ul style="list-style-type: none"> Provide expert technical and policy guidance on CPTR's strategy and goals. Help evaluate results.
CPTR Arms' Coordinating Committees	<ul style="list-style-type: none"> Provides the leadership for the arm Ensures flow of day-to-day operations and administration 	<ul style="list-style-type: none"> Interact with the CPTR Initiative Coordinating Group and ensures communication with the arm and workgroups
CPTR Arms	<ul style="list-style-type: none"> Primary membership group for all stakeholders in the arm Coordinate among the arm's workgroups Decision-making body for the arm 	<ul style="list-style-type: none"> Identify the workgroups needed to reach its goals Work to ensure appropriate expertise needed for the workgroups Set the direction for the workgroups and coordinates among the groups
Workgroups	<ul style="list-style-type: none"> Conduct the technical activities of the subject areas within the arm 	<ul style="list-style-type: none"> Develop work scope for program area(s) Create the tools needed for advancing the arm's mission

Figure 4: CPTR Initiative Structure Key Roles

ETHICAL, SOCIAL, AND CULTURAL CONSIDERATIONS

OVERVIEW

ESC considerations touch many different facets of the CPTR Initiative. They include, but are not limited to: general ethical aspects of clinical trials; inclusion of particular patient populations (e.g., children, women of reproductive age) in clinical trials; the conduct of trials in countries with limited medical infrastructure; post-trial commitments of the sponsors; compensation of trial participants; compassionate use and early access; sharing, exportation and/or use of biological samples and data; use in future research; and, ethical underpinnings of effective community engagement. It will be critical to the success of the CPTR Initiative that these considerations receive due attention in tandem with scientific and regulatory advancements.

OBJECTIVES

The CPTR Initiative Coordinating Group will partner with an impartial organization having a global ESC perspective and expertise, in collaboration with other Initiative partners, to identify and address in culturally acceptable ways the anticipated and emerging ESC challenges that may arise in the context of the CPTR Initiative. These collaborative efforts will be enhanced through the involvement of ESC Program representatives within each of the three CPTR arms and in specific Workgroups in which ESC challenges are deemed most likely to arise (e.g., Stakeholder and Community Engagement, and Access

and Appropriate Use Workgroups under the Research Resources arm). These integrated interactions will enable the development and dissemination of tailored, practical strategies to address potential ESC challenges along the critical path.

SPECIFIC TASKS

The specific tasks of the CPTR Initiative’s ESC efforts include:

- Proactively identifying potential ESC challenges within the CPTR Initiative
- Initiating dialogue around those challenges
- Developing strategies to address ESC barriers along the critical path
- Communicating the findings and conclusions across the Initiative to the global health community.

CPTR REGULATORY SCIENCE CONSORTIUM

To undertake the CPTR Initiative’s ground-breaking approaches, the CPTR Consortium participants will need to share data, knowledge, investment, and scientific staff time.

The CPTR Consortium’s goals include:

- Integrating a combination development framework;
- Creating innovative tools; e.g., TB data standards, databases, biomarkers and clinical endpoints, clinical disease progression models for use in researching and developing drugs, and drug regimens for the treatment of TB;
- Establishing consensus among scientists from industry, academia, regulatory authorities, and other government agencies regarding preferred tools for developing TB drugs and drug regimens; and
- Obtaining qualification of such tools for specific context of use from regulatory authorities.

CPTR Consortium participants will suggest and enable the use of these tools across the spectrum of combination drug development as envisioned for the CPTR Initiative (Figure 5). Additionally, an ultimate goal is to advance the TB regimens development process generally through broad public dissemination of the results of the Consortium’s efforts.



Figure 5: Schematic Representation of TB Drug and Drug Regimen Development Phases

C-Path has established a legal framework that allows data sharing among scientists from multiple pharmaceutical companies, academia, and regulators such as FDA and EMA, as well as other government agencies. Organizations that are signatories to the legal agreement become voting members of the CPTR Consortium. Confidential disclosure agreements will provide an effective mechanism for scientists from non-government organizations, academic researchers, and other experts to participate as advisors. Government scientists will be able to participate under authorization from agencies that have submitted a letter of participation or a memorandum of understanding.

Section 3 of this Work Scope outlines the work products and process for the Workgroups. Consortium members will contribute expertise to as many of the Workgroups as possible. Each Workgroup will develop a work plan to establish criteria, prepare an inventory, evaluate data, and develop consensus. The Workgroups will collaborate in preparing data submissions to the FDA Biomarker Quality Review Team and to EMA Scientific Advice Working Party through the Novel Methods Qualification Procedure for their assessment and decision as to whether the biomarkers are “qualified for use” or if clinical disease models are ‘suitable for the stated purpose’ in TB drug development (Figure 6).

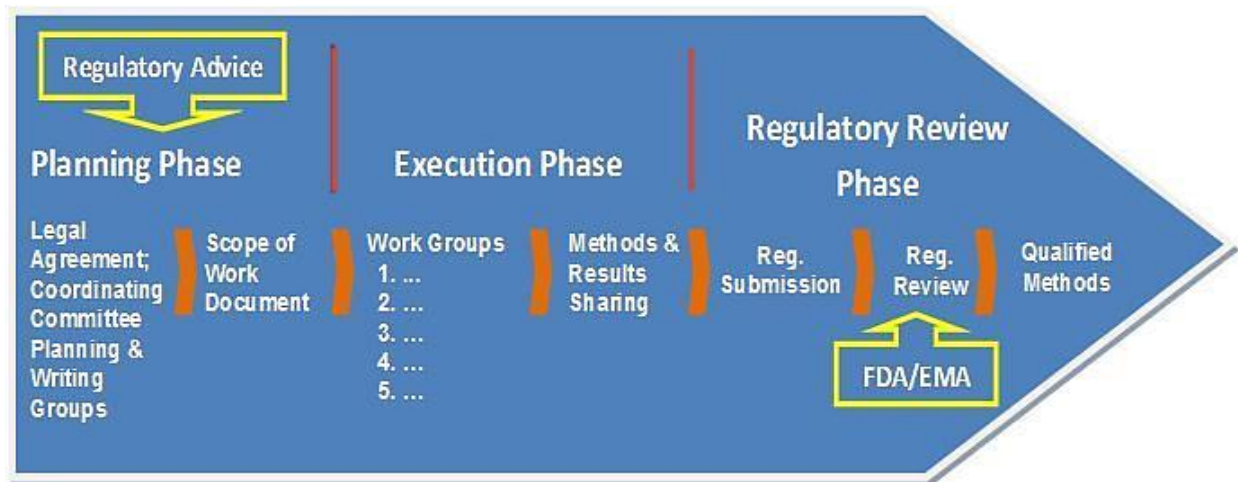


Figure 6: CPTR Regulatory Science Consortium Roadmap (“Regulatory Advice”--Includes FDA and EMA)

PROCESS FOR BIOMARKER QUALIFICATION

To undertake the CPTR Initiative’s ground-breaking approaches to advance TB drug development, the CPTR Consortium participants will need the ability to share data, knowledge, investment, and scientific staff time. Each Workgroup will develop a plan to establish criteria for decision-making, prepare an inventory, evaluate data, and develop consensus. Once consensus has been reached, the Workgroups will collaborate in preparing data submissions to the FDA’s Biomarker Quality Review Teams and to EMA’s Scientific Advice Working Parties through the Novel Methods Qualification Procedure for their assessment and decision as to whether the biomarkers are “qualified for use” or if clinical disease models are ‘suitable for the stated purpose’ in TB drug development. Figure 6 schematically describes the process that C-Path has helped develop by working with the FDA, EMA and PMDA for the qualification of biomarkers.

C-Path has used its experience in preparing data submission packages for biomarker qualification by the FDA to prepare a “roadmap” that will facilitate the efficient preparation of such submissions for this work. Specific steps in the qualification submission roadmap are presented in Table 1. While useful as a checklist, the roadmap must be customized to the specifics of each biomarker and the context in which it is expected to be used. In all cases, the value of formal and informal participation of domain experts and of regulatory scientists will be essential.

FDA has encouraged the development of biomarkers as potentially powerful tools in drug development. The agency has established a pilot process for biomarker qualification, one which is also being used to qualify Patient Reported Outcome (PRO) instruments with C-Path’s PRO Consortium. Industry can rely upon using the biomarkers and PRO instruments in the qualified manner in regulatory submissions for new drugs, without needing to resubmit extensive data or reconfirm the biomarker’s value. Both FDA and EMA are currently establishing a review process for quantitative disease progression models being submitted by C-Path for Alzheimer’s disease.

TABLE 1: BIOMARKER QUALIFICATION SUBMISSION ROADMAP	
Stage 1. Establish biomarkers for qualification scope	<ul style="list-style-type: none"> 1.1 The Expert Panels will develop a candidate list of biomarkers to be qualified 1.2 Determine necessary assays / imaging methods to measure biomarkers 1.3 Develop biomarker context of use and claims 1.4 Identify initial data needed to support qualification
Stage 2. Finalize laboratory/pathology practices (if needed)	<ul style="list-style-type: none"> 2.1 Prepare a lexicon 2.2 Prepare a pictorial atlas for standardization of diagnoses and severity grading
Stage 3. Generate initial data	<ul style="list-style-type: none"> 3.1 Survey initial available data 3.2 Create statistical analysis team 3.3 Transmit initial data to C-Path in new CDISC format as needed 3.4 Complete initial analysis of existing data. Identify gaps
Stage 4. Write and review Research Plan	<ul style="list-style-type: none"> 4.1 Assemble Research Plan writing team from Expert Panel 4.2 Write Research Plan, w/ statistical analysis and assay characterization plans 4.3 Submit for Working Group review 4.3 Submit for Advisory Committee review
Stage 5. Initiate formal contact with the regulatory agencies	<ul style="list-style-type: none"> 5.1 Write and review two-page letter of intent 5.2 Send letter of intent to submit a biomarker qualification package to FDA 5.3 Prepare and submit briefing document (research plan and cover letter) 5.4 Hold preliminary meeting with FDA and define path to submission

TABLE 1: BIOMARKER QUALIFICATION SUBMISSION ROADMAP

Stage 6. Execute biomarker qualification plan	
6.1	Collect additional data to fill gaps and in response to FDA initial meeting
6.2	Update research plan and resubmit if needed
6.3	Complete final data analysis for qualification submission
6.4	Characterize the technical performance of assays and imaging methods
Stage 7. Write and submit biomarker qualification package	
7.1	Create writing team and assign responsibilities
7.2	Write draft qualification package
7.3	Review and update by regulatory submission team
7.4	Review by workgroup and coordinating committee
7.5	Submit biomarker qualification package
7.6	Respond to questions, provide additional data requested by FDA

CPTR RESEARCH RESOURCES GROUP

The challenge of TB is already being addressed by a diverse global health community and we now must concentrate on creating new TB medical product development. Due to the complex nature of the organism, the disease and affected communities will also need substantial resources in order to make progress towards new TB therapeutics. The goals of the CPTR Research Resources Group are to work collaboratively with existing partners in the TB field to address challenges in regimen development, such as assessing existing clinical trial sites and supporting clinical trial site capacity-building; working with traditional funding streams and searching for new ones; soliciting global regulatory participation and solving regulatory challenges; developing support for procurement of and access to new TB drug therapies for patients in need; involving the TB stakeholder and the communities of TB patients and trial participants; and fostering access and appropriate use.

CPTR DRUGS COALITION

The CPTR Drugs Coalition brings together sponsor companies that have TB drug candidates in clinical development, sign the CPTR Statement of Principles, and agree to submit investigational TB drugs to be tested in combination—a process that could produce markedly improved, novel TB therapeutic regimens in years rather than decades. The CPTR Drugs Coalition’s goal is to rapidly develop highly effective TB therapeutic regimens using innovative methods generated by the CPTR Regulatory Science Consortium and resources secured through the Research Resources Group.

PROJECT MANAGEMENT AND COMMUNICATIONS

PROJECT MANAGEMENT AND ADMINISTRATION

OVERVIEW

The Project Management and Communications Team is responsible for supporting the overall CPTR Initiative. The Team will establish a project management staff support and infrastructure that will maintain project plans for each Workgroup, provide staff leadership, track progress, and provide status reports (the term *project management* also refers to the overall program). It will also facilitate collaboration and information-sharing across the CPTR Initiative.

SPECIFIC TASKS

The Project Management and Communications effort will:

- Provide overall coordination of Workgroup efforts
- Develop and maintain Workgroup schedules and milestones
- Maintain detailed work plans, schedule meetings, and document action items and project status
- Standardize general communication and collaboration tools
- Manage expenses and other resources
- Create templates and standard terminology for key documents
- Maintain a documentation database with appropriate security and document management controls
- Create and maintain a secure Web-based collaboration site for the CPTR Initiative using Microsoft SharePoint; this site will have a basic structure for communications within the Consortium, including:
 - A main page for announcements, general interest, and items of immediate interest
 - A section for each Workgroup where its members can post draft documents and share comments and resources
- Establish teleconference, Web conference, and videoconference capabilities as required to support the CPTR Initiative and its three arms

To review progress, C-Path will coordinate formal in-person annual meetings—and other meetings in the interim as needed—of the CPTR Initiative Coordinating Group. To keep Consortium members informed of progress on an ongoing basis, frequent communications will be conducted through email and other means.

EXTERNAL RELATIONSHIPS AND COMMUNICATIONS

OVERVIEW

The Project Management Support and Communications Team is also responsible for announcements and ongoing external communications of the CPTR Initiative's benefits and progress. External audiences will include the pharmaceutical industry, medical and business communities, regulators and legislators, and the media.

External communications will maximize the impact of CPTR’s announcements. This will include securing media coverage and industry/medical publication of significant accomplishments. This external communication is intended to generate significant visibility for CPTR and to lead to enhanced opportunities to bring additional support to the project.

OBJECTIVES

The objectives of the external relationships and communications effort are to:

- Build awareness and credibility of the CPTR Initiative
- Support resource mobilization efforts

SPECIFIC TASKS

The specific tasks of the external relationships and communications effort include:

- Developing internal and external communication documents as needed
- Writing content for website
- Developing necessary collateral materials
- Creating branding for the Initiative
- Developing press strategy and leading the execution of any announcements

CPTR REGULATORY SCIENCE CONSORTIUM

MISSION & GOALS

The CPTR Consortium’s overarching aim will be to submit the evidence necessary for regulatory authorities (e.g., FDA and EMA) to officially review and designate testing methods as “qualified or fit for use” in drug development. The newly qualified regulatory science testing methods will then be made available for the Drug Coalition to use and made public for scientists and commercial developers to employ.

CPTR REGULATORY SCIENCE CONSORTIUM WORKGROUPS

It is proposed that several Workgroups (listed below) be formed initially to focus on specific projects that will provide data to support the above goals:

- Integrated Sciences
- Data Standards and Integration
- Biomarkers and Clinical Endpoints
- Preclinical and Clinical Sciences
- Clinical Disease Progression Modeling
- Health Authorities Submissions

These Workgroups may be modified and/or other Workgroups created as the CPTR Consortium determines necessary. A C-Path support team will provide project management, logistical, and communications support.

The following sections outline the function of the CPTR Consortium Workgroups, which are described in detail in sections 3.3 through 3.7.

WORKGROUP 1: INTEGRATED SCIENCES TEAM

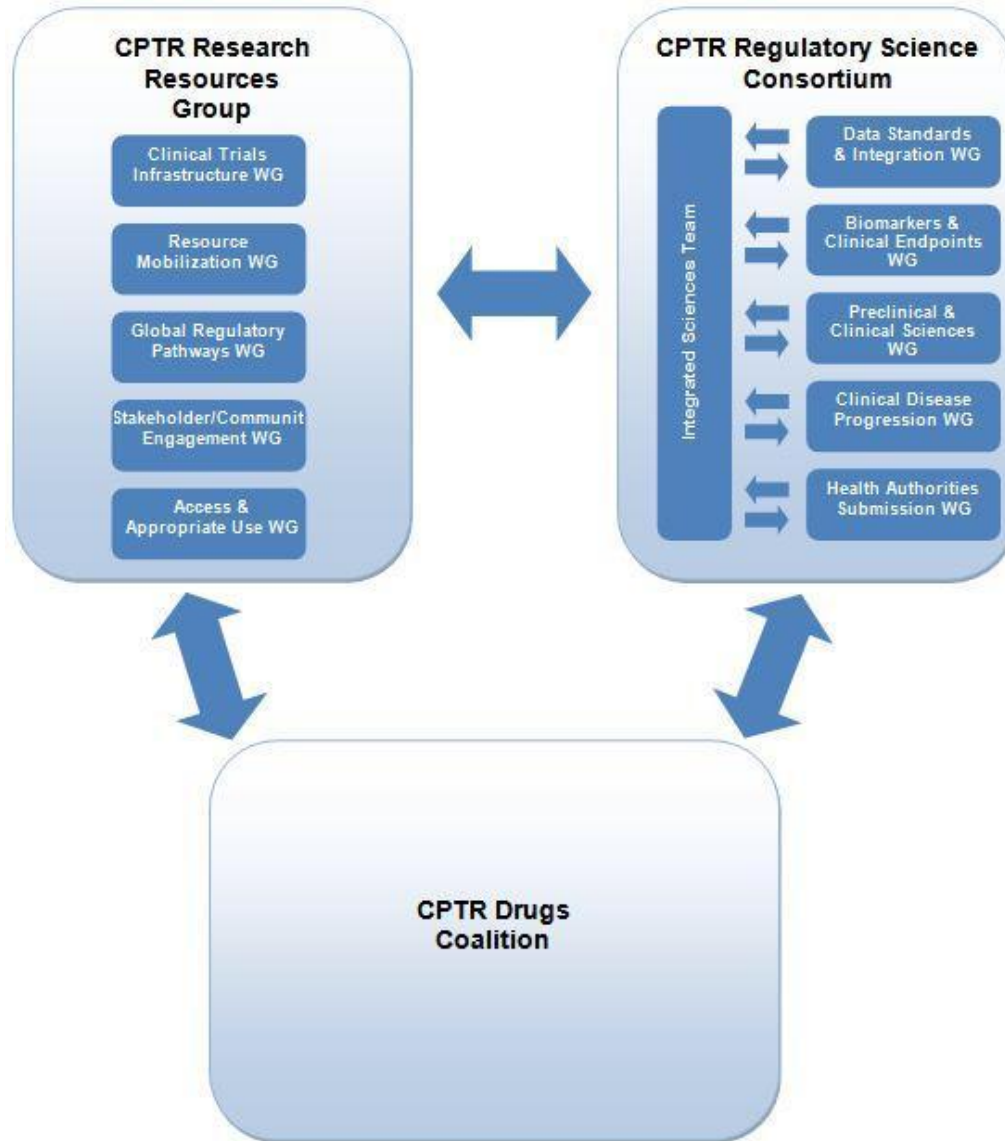


Figure 7: Relationship Among the Integrated Sciences Team and the Individual Workgroups Within the Regulatory Science Consortium and with the CPTR Drugs Coalition and CPTR Research Resources Group

OVERVIEW

The primary responsibilities of the Integrated Science Team (IST) will involve coordination and alignment of activities within the five regular Workgroups of the Regulatory Sciences Consortium to best meet the goals of the CPTR Initiative. Furthermore, the Team will facilitate seamless communication with the CPTR Drug Coalition to best secure the needs of the latter are optimally addressed (see example below), and with the CPTR Research Resources to communicate resource and funding needs. Thus, the role of this Team, in contrast to the regular Workgroups, is principally one of active coordination, alignment and facilitation, and differs from that of the Coordinating Committee of the Regulatory Science Consortium, which plays more of an oversight role. Considering the roles and responsibilities of the IST, the members will include the Leaders of each of the five regular Workgroups; other members may be added as warranted at a later time. The two Co-leaders of the IST will be from C-Path and TB Alliance.

PROCESS

The CPTR Drugs Coalition and the IST, in concert with the appropriate Workgroup, will identify the need for qualified tools and methods for any of the stages of regimen development and coordinate the work required to fulfill that need. For example, the Drugs Coalition may need a rapid, point of care diagnostic that could be qualified for use in an early bactericidal activity trial to rapidly identify patients qualified for enrollment. The IST would then communicate this need to the relevant workgroups and coordinate their work and the qualification process; the following steps would be likely:

1. The IST would notify the Biomarker and Clinical Endpoints Workgroup of the need for a biomarker and its likely context of use.
2. Alert the Data Standards and Integration Workgroup that new data elements will be needed for the new TB diagnostic biomarker.
3. Alert the Health Authorities Submission Workgroup that a qualification request for the new diagnostic biomarker will be forthcoming.
4. The Health Authorities Submission Workgroup will initiate communication with Health Authorities to begin planning for the qualification process and negotiate the context of use.
5. The IST will monitor the process and communicate resource and funding needs to the Coordinating Committee.
6. The IST will communicate all progress, problems, and issues that arise during the process to the Drugs Coalition and to the Coordinating Committee.

Other responsibilities of the IST will include continuously assessing any Regulatory Science needs for the CPTR Initiative that may surface, in addition to regulatory qualification processes, and making recommendations how best to address these. Such recommendations would typically be made to the CPTR Initiative Coordinating Group, and might include any aspects related to discovery or development of TB drugs, scientific or technical issues.

WORKGROUP 2: DATA STANDARDS AND INTEGRATION

OVERVIEW

The primary goal of this Workgroup is to collect data in a standard format to help with analysis and regulatory review. The Workgroup will address two primary objectives: 1.) to provide the infrastructure/architecture of the entire Information Technology (IT) system for the CPTR Consortium, and 2.) to convert all data domains and individual data elements requested by the other Consortium Workgroups to a standard usable format to populate the integrated database.

The Data Standards and Integration Workgroup will focus on having the data from TB clinical trials conform to an accepted, standardized format to help with analysis and regulatory review. The first steps will be to review of the Clinical Data Interchange Standards Consortium (CDISC) TB data standards and identify additional data elements that will be needed. Regarding existing data, the Data Workgroup will first compile and convert source data into a standardized format for semantic interoperability and integration into the other Workgroup activities and then maintain the IT infrastructure through C-Path. The data requirements refer to those individual elements or domains deemed necessary by the Workgroups to draw meaningful scientific conclusions, and should therefore be considered deliverables of those Workgroups. It will be important to establish best practices standards for both data mining/modeling and reporting models.

These standards are important considerations in setting the framework for how tasks will be accomplished and will likely evolve over time. When considering the various data needs of the CPTR Consortium, it is important to distinguish between data requirements of the Workgroups, the standards for collecting and integrating the data, the requirements for data storage infrastructure, and the tools for data analysis.

The Data Standards and Integration Workgroup will work with national standards organizations, such as CDISC and Health Level 7 (HL7), to ensure that its efforts are aligned with the standardization efforts currently being developed and implemented by the FDA and in the pharmaceutical and, if possible, healthcare industries. The Workgroup will work with regulatory authorities (e.g. FDA and EMA) to ensure all data for the CPTR Initiative are formatted in a manner that is easily accessible by the agency.

PROCESS

The Workgroup will address the technical requirements of gathering, assessing, standardizing, and pooling disparate sources of clinical and laboratory data into an integrated database (Figure 8). It will enable the efforts of the other Workgroups and will be accomplished by obtaining input on their needs and priorities and then working with member companies, National Institute of Allergy and Infectious Disease (Division of Acquired Immunodeficiency Syndrome and Division of Microbiology and Infectious Diseases), Centers for Disease Control (CDC) and other sources to compile information from the source data. The Data Workgroup will describe the work needed to develop standards for remapping and integrating data from a variety of sources and formats into a common format based on open, consensus-based standards where feasible (e.g., CDISC and HL7). It also addresses how the Consortium will integrate, submit, store, access, and analyze the data in a centralized system.

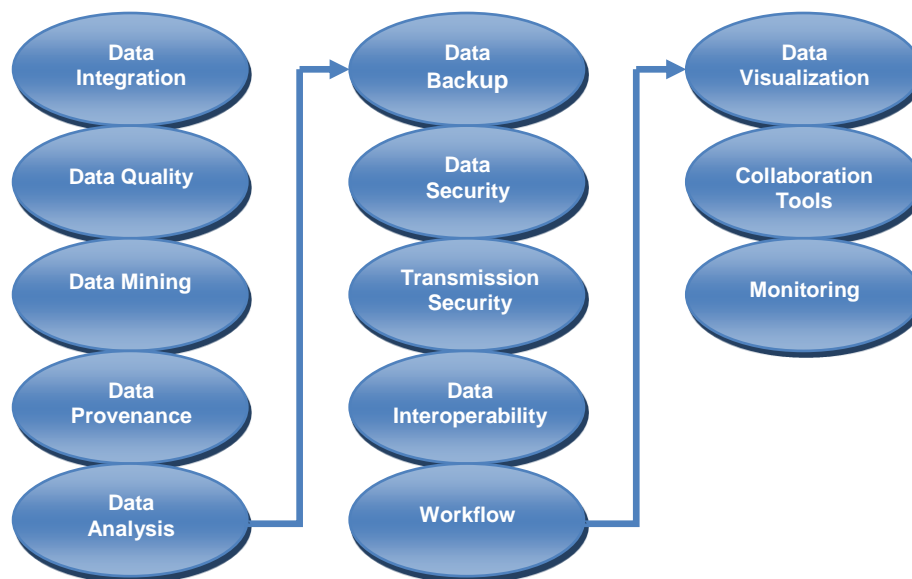


Figure 8: Data Infrastructure Goals

In support of these objectives, the Data Standards and Integration Workgroup will:

- Make linkages to key personnel of the data holders to collect the relevant information
- Develop data usability criteria in consultation with the CPTR Consortium’s Workgroups
- Use these criteria to assess fitness of candidate source data for inclusion in the project
- Work closely with the CPTR Consortium Workgroups and others as needed to understand their evolving data needs so that data conversion can occur in a timely manner
- Address quality control throughout the process of data conversion
- Coordinate submission of data to appropriate regulatory authorities for review
- Evaluate and recommend potential hardware and technology products and vendors for their ability to meet the security and functionality requirements
- Assist in decisions on available commercial off-the-shelf analysis tools, or to develop custom analysis tools that will fit the requirements of the project

WORKGROUP 3: BIOMARKERS AND CLINICAL ENDPOINTS

OVERVIEW

The Biomarkers and Clinical Endpoints Workgroup will identify, develop consensus, and build the evidence base to submit potential biomarkers and clinical endpoints that have promise in the development of new TB medical products to FDA and EMA for qualification in a specific context of use.

A traditional diagnostic for TB has been the sputum smear and culture. Disease response has been assessed by measurement of *Mycobacterium tuberculosis* in sputum from pulmonary TB patients and quantification of *Mycobacteria* has been one method used to evaluate drug efficacy.

The focus of the CPTB Biomarkers and Clinical Endpoints Workgroup will be to establish and execute a plan for compiling, reviewing, and evaluating the scientific merit of biomarkers and clinical endpoints for disease detection, activity, progression, prediction of response to treatment, and safety, including molecular, immunologic, genetic, and imaging data, which are potentially useful in TB drug development and regulatory review. Initially, data format and requirements will be established through collaboration with the Data Standards and Integration Workgroup.

PROCESS

The Biomarker and Clinical Endpoints Workgroup will establish and execute a systematic process for collation and review of candidate molecular, immunologic, genetic, and imaging biomarkers and clinical endpoints to evaluate the supporting scientific merit/strength of evidence.

The work will begin by: 1.) identifying data sources for candidates biomarkers and clinical endpoints; 2.) compiling a comprehensive list of the existing scientific literature, ongoing research, and established databases; 3.) incorporating into disease-progression models and internal CPTB member unpublished data and published reports (Figure 9). The first phase of this biomarker and clinical endpoint review effort will define the process for prioritizing candidates, determining criteria for evaluation, and establishing the method of rating the degree of confidence in each biomarker and clinical endpoint according to established methods of review. The specific context of use for each biomarker and clinical endpoint will need to be explicitly defined.

The second phase will be to evaluate evidence and select the most promising biomarkers and clinical endpoints for regulatory review, qualification for specific use contexts (where appropriate), and acceptance and use by the scientific community for a specific purpose. Evidence will be thoroughly reviewed, including rigorous statistical analysis of data. Candidates will be ranked, and evaluation of the top-tier will continue with formulation of the claim of specific purpose(s) for each biomarker or clinical endpoint, review of evidence supporting claims, and identification of gaps in supporting evidence. A clinical validation program, for either de novo and/or re-mining of retrospective data, will be designed. It is desirable to develop clinical program templates that can be used as a tool to guide clinical program development in a standardized approach, but it is also anticipated that the specific program for qualification will be a biomarker or clinical endpoint and drug development claim-specific. When claims are determined to be adequately supported by evidence, these will be considered for submission to the FDA Biomarker Qualification Review Team and EMA Novel Methods process.

Working together with the Data Standards and Integration Workgroup, information management also will be addressed, including development of a standardized format for the biomarker and clinical endpoint evidence database, as well as the infrastructure and method for storage and sharing of candidate information. This process is open and dynamic, with data supporting candidate biomarkers and clinical endpoints entering the evaluation process on an ongoing basis. As data become available, the Workgroup will re-evaluate them and reprioritize biomarkers and clinical endpoints based on

cumulative evidence. Additionally, biomarker and clinical endpoints data will be integrated into clinical disease progression models, and evolving clinical disease models will be used to help with the evaluation of biomarkers and clinical endpoints.

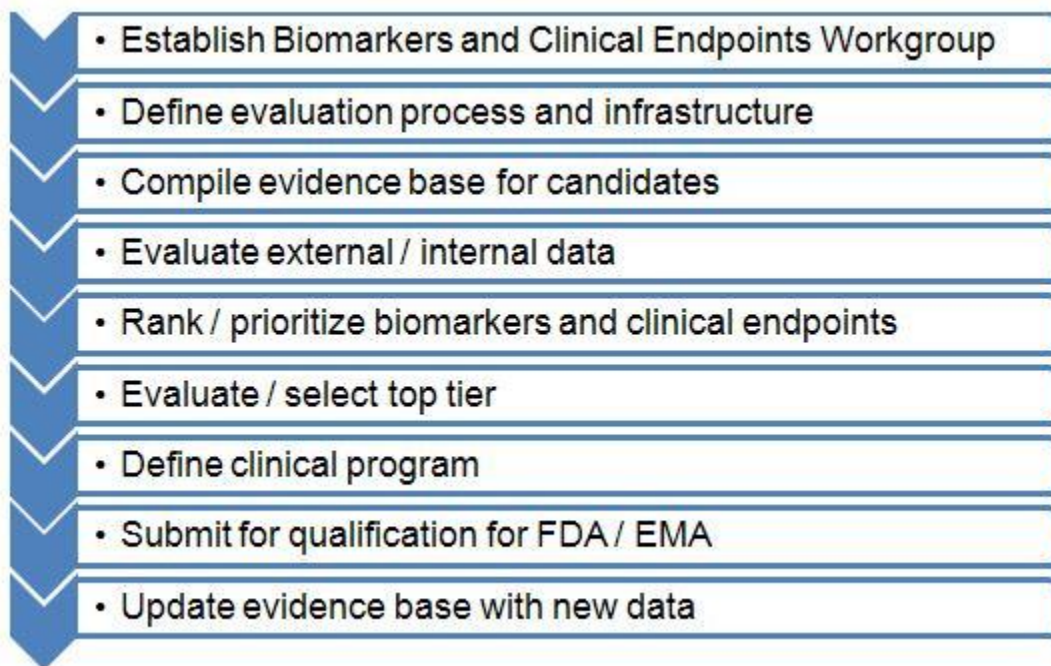


Figure 9: Biomarker and Clinical Endpoint Process

WORKGROUP 4: PRECLINICAL AND CLINICAL SCIENCES

OVERVIEW

The Preclinical and Clinical Sciences Workgroup will focus mainly on developing qualified tools and innovative approaches to address preclinical issues, including preclinical in vitro and in vivo efficacy, preclinical drug safety and toxicology, preclinical PK/PD analyses involving the use of appropriate biomarkers, preclinical drug metabolism and drug interaction potential, and pharmaceutical profiles. This Workgroup will also cover other issues as pharmaceuticals, clinical PK/PD analyses of concentration vs. pharmacologic response data from clinical studies.

Many of these approaches will continue to evolve over the next several years, and new innovations are likely to include more predictive preclinical efficacy models and novel biomarkers with rapid readout. Specific additional preclinical experiments needed for pre-IND packages of the individual candidates to enable regimen development also need to be identified.

PROCESS

The Preclinical and Clinical Sciences Workgroup will function with the other Workgroups, particularly those focused on Biomarker and Clinical Endpoints and the Integrated Regimen Development Framework. This may be accomplished through two or more well connected subgroups.

A key focus will be those components of the pre-IND packages that support successful clinical regimen development. The specific topics include those in the paragraphs below, but other topics may be added as appropriate.

Preclinical in Vitro and in Vivo Animal Models—The most widely used preclinical efficacy models—different mouse and guinea pig models—have their strengths and weaknesses. The most significant limitations involve their long duration of testing, persistent TB bacteria, and differences in animal vs. human pathology. There is therefore a great interest in the development of models with faster readouts and more human-like pathology. Examples include the *ex vivo* whole blood culture infection model to better understand non-replicating TB bacteria profiles, artificial granulomas, and the application of other species. This Workgroup will evaluate the evidence base and develop criteria for the utility of the various preclinical models to test new drug candidates.

Preclinical Drug Safety and Toxicology—In addition to the regulatory mandated preclinical drug safety and toxicology studies on the individual TB drug candidates, careful assessment is required of the preclinical profiles of proposed combination products, specifically with respect to overlapping organ toxicities. Depending on their nature and extent, separate preclinical combination experiments may be warranted.

Drug Metabolism and Potential for Drug Interactions—In addition to standard preclinical approaches to characterize the drug metabolism profile and routes of elimination of individual TB drug candidates, as well as testing for the potential for drug-drug interactions, based on *in vitro* CYP and transporter testing, additional *in vitro* and *in vivo* combination experiments may be warranted. Also, approaches to predicting drug-drug interactions in humans, e.g., physiologically based (PB) PK methods, need to be considered.

Preclinical and Clinical PK/PD Modeling and Simulation—In addition to standard preclinical PK assessments in appropriate species, special effort will be devoted to preclinical PK/PD modeling and simulation to better understand exposure vs. response characteristics and tissue distribution to the sites of infection for the individual TB drug candidates. Of interest will be drug uptake into granulomas, including the potential use of bioimaging approaches. During clinical combination product development, PK and PD data will be collected in a variety of individual and combination trials to develop appropriate exposure vs. efficacy models, including the application of population PK/PD methodologies.

Pharmaceutics and Formulation—Consideration needs to be given to the optimal formulation approaches for the individual TB drug candidates, based on their pharmaceutical properties.

Preclinical and Clinical Sciences Knowledge Gaps—This Workgroup will also make an assessment of the available preclinical and clinical data on the currently available TB drugs. Considering that these are decades old, it is likely that data that would be required for new TB drug candidates today will not be available for these agents. Therefore, this Workgroup will make a determination as to what specific knowledge gaps exist regarding old TB drugs, and will make recommendations as to how these can be filled if deemed critical for the success of the CPTTR project.

WORKGROUP 5: CLINICAL DISEASE PROGRESSION MODELING

OVERVIEW

This Workgroup will use pooled data from the Data Standards and Integration Workgroup to create robust (in terms of scope and predictive accuracy) clinical quantitative disease-progression models for use in TB regimen development. The data used to create such models will be pooled from clinical trials performed by CPTDR Drug Coalition member companies and other sources. Additional data on relevant biomarkers (e.g., laboratory tests, imaging parameters, microbiology assays, etc.) and clinical endpoints will be progressively incorporated into the models as they are generated by the respective team of the coalition.

The primary use of the clinical disease progression model will be to inform clinical trial design. Such an approach can be used to characterize and quantify natural disease progression, placebo and drug effects, informed dose selection, as well as trial execution variables (e.g., patient discontinuation rates, dosing schedules, compliance, self medication, specific design, etc.) from multiple trials using patient-level data.

These models can increase efficiency and decrease risk of errors in drug-development decisions by overcoming the complexity and uncertainties of the disease-drug-treatment interaction. Many factors that influence outcomes can be considered simultaneously with the use of simulations and the weight of knowledge and data gaps may be more systematically ranked and prioritized. A model-based drug-development approach can increase efficiency by integrating all pertinent prior information into a predictive model, which in turn can guide the design of clinical trials and drug development strategy.

This Workgroup will describe: 1.) the application of mathematical models to characterize TB clinical disease progression, and 2.) how the modeling process is a continuum that begins with existing knowledge and evolves as more data becomes available. As further knowledge regarding preclinical models, biomarkers, imaging parameters, microbiology assays, mechanistically defined subpopulations, and pharmacology become incorporated into the model and associated with clinically relevant outcomes, it will be possible to examine potential relationships and associations.

Once the model contains sufficient information about the complex interactions between parameters in the models, a systems dynamics approach can be applied to create whole system biology models. Criteria can then be established for consensus identification of candidate parameters (e.g., biomarkers, imaging, assays, models, discrete patient subsets, etc.) that can be submitted to the FDA and EMA with a request that they be deemed “qualified” for specific use(s) in drug development. The subsequent results from the parameter’s “use” in drug development can be considered “learning” or confirmation of knowledge that is then incorporated into the whole systems biology models with the purpose of enriching the model and improving its predictive accuracy.

PROCESS

The Clinical Disease Progression Modeling Workgroup will:

- Describe modeling techniques and their context of application

- Describe how and when those modeling techniques could be applied to generate robust clinical quantitative disease-progression models for use in drug development for TB
- Define the clinical trial endpoints that will be incorporated into the model
- Evaluate the level of correlation among multiple covariates
- Evaluate the longitudinal predictability of each scale and its applicability in drug development
- Identify prospective or retrospective datasets that will inform the model development
- Design a predefined model scope, as well as a data and knowledge analysis plan for all drug response and disease scales of interest
- Design a predefined plan for model development, evaluation, calibration, and implementation
- Continuously incorporate candidate biomarkers and clinical endpoints of disease stratification, activity/severity, and progression for drug susceptible TB
- Address the effects of patient compliance on the trial outcomes

The process to develop robust quantitative disease models will follow a downwardly integrative approach, beginning with empirical models based on clinically observed phenomena (Figure 10).

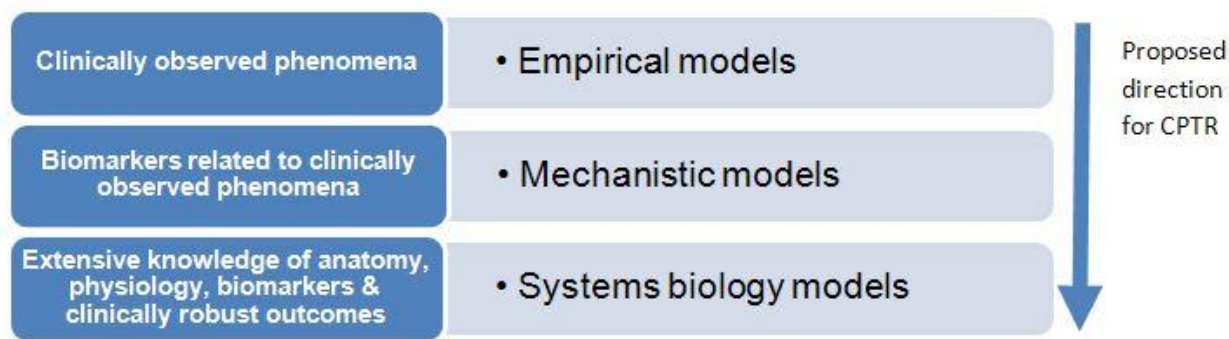


Figure 10: Clinical Disease-Progression Modeling

WORKGROUP 6: HEALTH AUTHORITY SUBMISSIONS

The Health Authorities Submissions Workgroup has as its mandate managing the interface between the other Workgroups and health authorities. This team does not develop or analyze data or models, but rather assures that the progress of these efforts is informed by current thinking within health authorities. Importantly, when such data or models reach a level of maturity as to warrant regulatory review, the Health Authorities Submission Team will be responsible for:

- Seeing that the collation of such information is ready for submission to the health authorities; and
- Preparing the submission package, following current submission policies and procedures and serving as the primary interface for communication between the CPTR and the health authorities during the review process.

INITIAL PROJECT TIMELINE

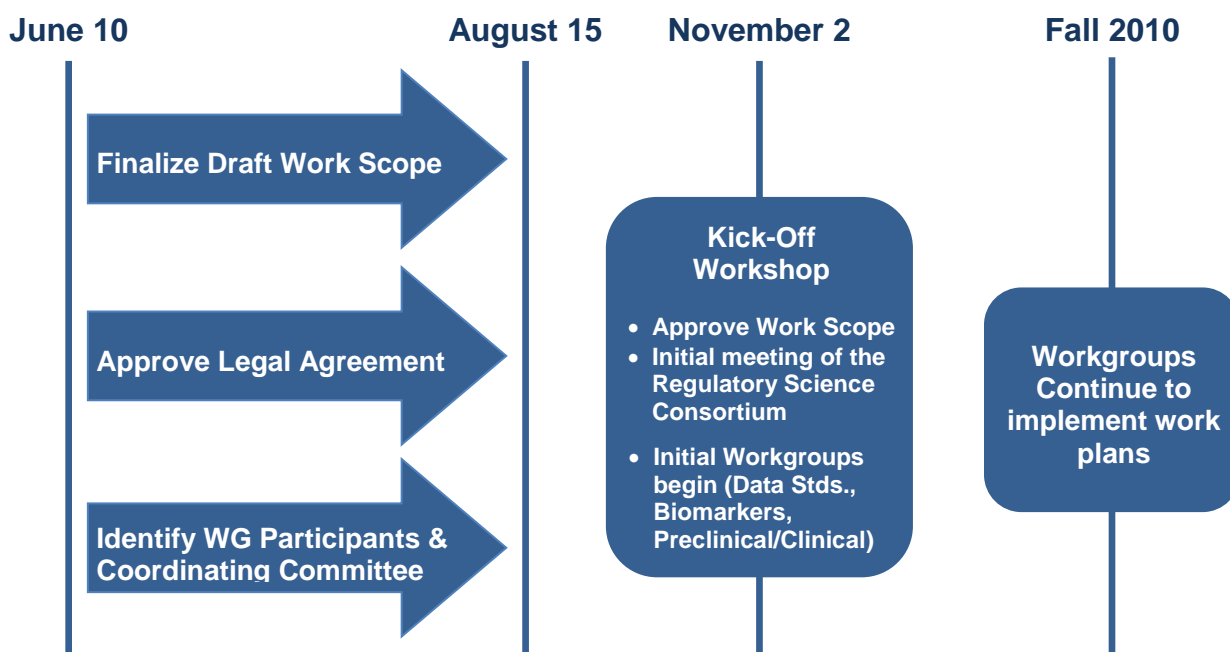


Figure 11: Initial CPTR Regulatory Science Consortium Timeline

CPTR DRUGS COALITION

The CPTR Drugs Coalition will facilitate the ability of sponsors of potential TB drugs to work together on rapid clinical development of optimized regimens. The present clinical pipeline of potential TB drugs is the largest ever. However, it is characterized by having multiple sponsors, with no single sponsor being in the position of having either enough molecules or enough resources to complete clinical development and global registration of optimized, novel regimens. Therefore, the need has arisen for a vehicle such as the CPTR Drugs Coalition, through which TB drug sponsors can make informed decisions concerning the regimens in which they wish to participate.

The CPTR Drugs Coalition will consider the following in developing its operating principles:

- Only those institutions that have potential TB drugs in clinical development will be members of the Coalition; other institutions and individuals will be invited to participate in the Coalition’s activities and meetings at the discretion of the members.

- The prime function of the Drugs Coalition will be to share preclinical and clinical data on the compounds under development. Such sharing will be done under confidentiality agreements.
- Such sharing of data is designed to facilitate independent decision making on the part of the respective sponsors as to which regimens appear to be most promising.
- There will be no discussions or decision-making within the Drugs Coalition regarding any aspects of commercialization of either drugs or regimens.

Once the legal framework for the CPTR Drugs Coalition is agreed to, the Coalition members will finalize both the details of the work scope and further operating principles.

CPTR RESEARCH RESOURCES GROUP

MISSION & GOALS

The CPTR Research Resources Group has been created to increase the likelihood of successful innovative TB drug development by creating a framework and infrastructure that will support the development of novel TB regimens, including:

- Increasing clinical trial capacity
- Raising funding for late stage clinical development (Phase II and III)
- Promoting understanding of the potential ESC challenges along the critical path to TB drug development
- Expanding regulatory guidance globally
- Providing relevant information on TB drug markets and their complexity
- Ensuring effective and appropriate stakeholder and community engagement

The CPTR Research Resources Group's approach is multifaceted in fostering an environment for successful innovative TB drug development. The Group will work collaboratively with experts from many partners to address together the challenges of building the clinical trial and laboratory site capacity and quality; funding for late stage clinical development of TB drugs; global regulatory pathways in developed, developing and underdeveloped countries; access and appropriate use of novel TB drug regimens; and the complexity of TB drug markets.

The Research Resources Group will support efforts that meet the following criteria:

1. Address a significant hurdle in the critical path to regimen development and not already addressed by the other two Workgroups,
2. Create efficiencies across the CPTR Initiative, and
3. Increase the likelihood of success of TB regimen development.

CPTR RESEARCH RESOURCES WORKGROUPS

Several proposed CPTR Research Resources Workgroups have been identified to conduct tasks related to various projects as defined below. These Workgroups may be modified, and other Workgroups created, as the Research Resources group determines necessary.

WORKGROUP 1: CLINICAL TRIALS INFRASTRUCTURE

OVERVIEW

The Clinical Trials Infrastructure Workgroup will identify efficiencies across clinical trial sites and support a coordinated approach to clinical research for TB regimen development. Because a registration trial for a novel TB drug has not been done for many years, there is the need and opportunity now to build capacity in existing TB clinical trial and laboratory sites.

In order for the CPTR Initiative to achieve success, training and coordination of the clinical trial infrastructure will ensure that the sites are prepared to conduct high quality GCP registration trials. In order to preserve capacity, it is necessary that only the most essential trials take place. This will build on already existing work in the drug development space, and take into consideration the assessment of clinical trial sites and their capacity, identified needs and opportunities for capacity building at clinical trial sites.

PROCESS

The Clinical Trials Infrastructure Workgroup will consist of members of organizations that have endorsed the CPTR statement of principles and who work or could contribute to developing, maintaining and sustaining clinical trial infrastructure, including laboratory capacity. The Workgroup will work with existing efforts to identify an approach that builds on that already underway by CDC, WHO, NIH and others.

WORKGROUP 2: RESOURCE MOBILIZATION

OVERVIEW

The Resource Mobilization Workgroup will assess, analyze, evaluate, and communicate the costs of regimen development and the potential return in an effort to identify both traditional funding opportunities and novel financing opportunities for regimen development partners.

Current estimates for the development of a drug regimen are approximately \$700M over the next ten years. Approximate per patient clinical trial costs range from about \$20K to over \$100K and are escalating rapidly. Many of the member organizations and companies are contributing funding for early stage clinical trials (up through Phase IIB). However, resource gaps are expected—particularly during the later stage clinical trials (Phase IIB and III)—and will need to be filled for registration and licensure. This effort will build on existing efforts by companies already conducting trials, and organizations that are currently estimating funding requirements and resource gaps for product development in TB.

PROCESS

Members of the Resource Mobilization Workgroup will consist of donors, advocates, business development, and finance experts who will work together to support the financial planning and analysis needed for targeted and innovative resource mobilization across CPTR partners.

WORKGROUP 3: GLOBAL REGULATORY PATHWAYS

OVERVIEW

The Global Regulatory Pathways Workgroup will identify efficiencies in the regulatory pathway to develop a novel regimen. This could include fostering dialogue among key regulatory agencies, WHO, and NTPs, or it may focus on promoting the development of a pathway for regulatory approval that incentivizes regimens development. Regulators from countries or regions with high TB burden will be included in this process.

Because of the nature of TB, the CPTR Initiative's goal is to foster development, testing and regulatory review of a novel regimen containing multiple compounds. Regulatory pathways will need to be defined in order to accelerate this process.

PROCESS

The Global Regulatory Pathways Workgroup will determine priority areas for engagement on regulatory efforts. They will receive input from other Workgroups, including working closely with the Regulatory Science Consortium and Drugs Development Coalition. Members of this Workgroup will be experts in developing regulatory strategies for their companies or organizations, representatives of regulatory agencies, and other relevant experts on regulatory affairs.

WORKGROUP 4: STAKEHOLDER AND COMMUNITY ENGAGEMENT

OVERVIEW

The Stakeholder and Community Engagement Workgroup will facilitate the development of regimens by early, effective, and appropriate collaboration of key stakeholders and by building awareness and support among communities. The ability to successfully engage the community while conducting clinical trials is an essential component for regimen development.

PROCESS

Members of the Stakeholder and Community Engagement Workgroup may be called upon to present on regimen development in key meetings, contribute to guidance documents, or help address specific questions that may arise in the context of an ongoing trial or CPTR-related activity. This Workgroup will consist of experts in stakeholder and community engagement.

WORKGROUP 5: ACCESS AND APPROPRIATE USE OF NEW DRUGS

OVERVIEW

The Access and Appropriate Use Workgroup will identify areas of missing evidence or expertise that may become a barrier on the critical path to the launch plan. This Workgroup will also help address questions

of access or availability to drugs while they are in development. Additionally, it will establish a framework for dissemination and appropriate use once the new regimen is approved and marketed.

While a new CPTR regimen is more than five years away, it will be important to develop a strong evidence base and criteria to support access and appropriate use once a regimen is approved and ready for use. In addition, it is likely that within two to three years, two new drugs will be approved for MDR with a limited data package in areas important to the CPTR Initiative.

PROCESS

Members of the Access and Appropriate Use of New Drugs Workgroup will work with the CPTR Drugs Coalition, as well as with targeted countries, to identify priority areas for further work. The potential scope of the projects and work may include manufacturing capacity, supply chain analyses and problem solving, market analyses, patient surveys, key decision-maker surveys, analyses of potential ESC challenges, policies on expanded access and distribution of the new drugs, etc. Members of this Workgroup will have expertise in various areas of access and appropriate use of TB drugs. They will likely come from the companies and organizations that are developing and marketing the TB drugs, as well as those with specific expertise in manufacturing, supply chain, users, and payers of TB drugs.

INITIAL PROJECT TIMELINE

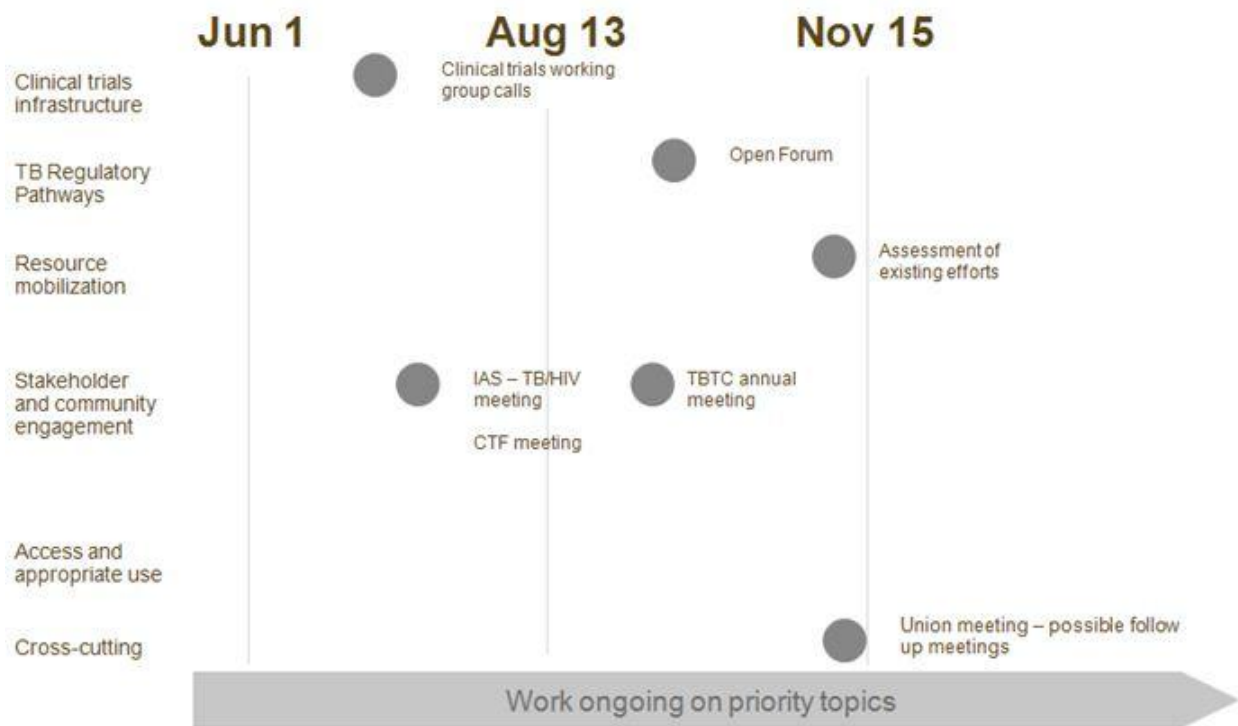


Figure 12: CPTR Research Resources Group Proposed Timeline