Critical Path to TB Drug Regimens Initiative

WORK SCOPE & INTEGRATED DEVELOPMENT PLAN

DRAFT
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Critical Path to TB Drugs Regimens

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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 launched on March 18, 2010, 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). CPTR works 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 accelerate development and review of new TB combinations.

The Critical Path Initiative 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 founded 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 CPTR initiative has evolved and expanded since its launch and initial mandate in 2010 and those updates are captured in this current work scope document and integrated development plan.

The Bill & Melinda Gates Foundation

Guided by the belief that every life has equal value, the 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.
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**

CPTR is one of seven consortia of C-Path, a nonprofit organization dedicated to accelerating drug development by delivering on the mission outlined by FDA’s critical path initiative. This mission includes 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 processes resulting in consensus among scientists from industry, government agencies, and academia, for preferred testing methods for new drugs, diagnostics, and devices; and
- Obtain regulatory qualification, where appropriate, of innovative testing methods.

C-Path’s consortia include more than a thousand participating scientists from numerous pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from regulatory agencies including the FDA, EMA, and the National Institutes of Health (NIH).

**Global Alliance for TB Drug Development**

The 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.

Since its founding in 2000, the TB Alliance has been a catalyst in 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 with 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 provides an unprecedented opportunity for a truly innovative approach.
CPTR was created to accelerate the development of new TB regimens by catalyzing innovative testing methods, product development partnerships, and novel development strategies. CPTR is managed by the Foundation, C-Path, and the TB Alliance. Within CPTR are four distinct components or “arms”: the CPTR Regulatory Science Consortium, CPTR Rapid TB Drug Susceptibility Testing Consortium (Rapid DST Consortium-launched in 2013), CPTR Research Resources Group, and CPTR Drugs Development Coalition (Figure 2).

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.

**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 and emerging data show that drug resistant forms of this disease are spread by primary contact. Eradication of TB disease will require the development of an effective vaccine, an entirely new drug regimen to treat resistant forms of the disease and an accurate diagnostic to aid support combination drug development as well as ensure that patients who need the new regimen are diagnosed before treatment with standard therapy. 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, with the exception of bedaquiline, which obtained accelerated approval for use in the most serious of MDR and XDR cases. 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. It is also imperative to protect the durability of new drugs, such as bedaquiline, by combining them with other novel agents rather than adding them to older drugs.

- **New, Innovative Models are Needed for TB Regimes 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.

**Principles**

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 collaboratively, 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

CPTR’s operational structure is built around its four arms: Regulatory Science Consortium, Research Resources Group, Rapid DST, and Drugs Development Coalition. The CPTR Working Group or ‘Leadership Team,’ comprised of staff members of the founding organizations, provides operational leadership and support by directing the overall CPTR policy and coordinating activities across the three arms (Figure 3). The Working Group also considers potential ethical, social, and cultural (ESC) challenges with the guidance of subject matter experts. The approach to how ESC challenges are addressed within the CPTR Initiative is outlined below.

Figure 3: CPTR initiative organization, structure and function
The Working Group receives strategy and policy-level guidance from the CPTR Advisory Panel, which includes invited leaders from across the TB drug development field: industry, regulatory, ethics, advocacy, global perspective, and philanthropy. The Panel meets in-person annually and by teleconference in the interim.

While the four operating arms tailor their specific structures to suit their missions, they generally operate through a set of workgroups under the guidance of the arm’s Coordinating Committee or the Working Group directly (Figure 2). Each arm determines its membership and workgroup participation criteria and operating procedures based on their needs and mission. All workgroups are led by (at least) two co-chairs, one from the membership and one staff representative.

**Ethical, Social, and Cultural Considerations**

ESC considerations touch many different facets of the CPTR Initiative: 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 is critical to the success of the CPTR Initiative that these considerations receive due attention in tandem with scientific and regulatory advancements.

The CPTR Working Group, through the Advisory Panel and in collaboration with other Initiative partners, identifies and addresses the anticipated and emerging ESC challenges that may arise in the context of the CPTR Initiative. These efforts are enhanced through the involvement of ESC Program representatives within each of the four 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, including:

- 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 CPTR’s ground-breaking approaches, the CPTR Regulatory Science participants need to share data, knowledge, investment, and scientific staff time. The Regulatory Science 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 or other levels of regulatory review and endorsement of such tools for specific context of use from regulatory authorities.

Consortium participants suggest and enable the use of these tools across the spectrum of combination drug development as envisioned for the CPTR Initiative (Figure 4). Additionally, an ultimate goal is to advance the TB regimens development process generally through broad public dissemination of the results of the Regulatory Science Consortium’s efforts.

C-Path has established a legal framework that supports protected data sharing among scientists from multiple pharmaceutical companies, academia, and regulators such as FDA and EMA, as well as other government agencies worldwide. Signatories to the legal agreement become voting members of the CPTR Regulatory Science Consortium. A confidential disclosure agreement is also used to 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.

Consortium member organizations contribute expertise to as many of the workgroups as possible. Each workgroup develops a work plan to establish criteria, prepare an inventory, evaluate data, and develop consensus. As appropriate to the specific tool, workgroups may also collaborate in preparing data submissions to the FDA and to EMA for their assessment and impact; e.g., whether the biomarkers are “qualified for use” or if clinical disease models are ‘suitable for the stated purpose.’ (Figure 5).
Process for Biomarker Qualification

To undertake CPTR’s groundbreaking approaches to advance TB drug development, CPTR Regulatory Sciences Consortium participants need to share data, knowledge, investment, and scientific staff time. Each workgroup develops a work plan to establish criteria for decision-making, prepare an inventory, evaluate data, and develop consensus. Once consensus has been reached, the workgroups may collaborate to prepare data submissions to FDA and to EMA 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 5 schematically describes the process that C-Path has helped develop by working with the FDA, EMA, and PMDA for qualifying biomarkers. In some instances, regulatory authorities may allow for and request alternate pathways for considering novel biomarkers or drug development tools. These mechanisms, including the Voluntary Exploratory Data Submission process and pre-IND avenue, are currently being employed by the Regulatory Sciences work groups.

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 for its described use. 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 have established a review process for quantitative disease progression models submitted by C-Path for Alzheimer’s disease.
Table 1: Biomarker Qualification Process Overview

| Stage 1. | Establish biomarkers for qualification scope |
| Stage 2. | Finalize laboratory/pathology practices (if needed) |
| Stage 3. | Generate initial data |
| Stage 4. | Write and review Research Plan |
| Stage 5. | Initiate formal contact with the regulatory agencies |
| Stage 6. | Execute biomarker qualification plan |
| Stage 7. | Write and submit biomarker qualification package |
| Stage 8. | Submit biomarker qualification package |
| Stage 9. | Respond to questions, provide additional data requested by FDA |

CPTR Research Resources Group

Due to the complex nature of the organism and the disease, 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 Development Coalition

The CPTR Drugs Development 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 Development 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

CPTR Operations

The project management and communications teams are responsible for supporting the overall CPTR Initiative. The teams will establish a project management staff support and infrastructure that will maintain project plans for each workgroup, provide staff leadership, track progress, provide status reports and facilitate collaboration and information-sharing across the CPTR Initiative.

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 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 coordinates monthly Working Group telecons, an annual workshop, and other meetings as needed. A quarterly workgroup report is also distributed to all CPTR participants.

External Relationships and Communications

The project management support and communications teams are 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 the media.

External communications will build awareness and credibility of CPTR and will support resource mobilization efforts. This includes securing media coverage and industry/medical publication of significant accomplishments. Specific tasks 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 Regulatory Science Consortium’s overarching is support the development of new TB drug regimens. This may include submitting the evidence necessary for regulatory authorities (e.g., FDA and EMA) to officially review and designate testing methods as “qualified or fit for purpose” 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.
Workgroups

The following workgroups have been formed to focus on specific projects that will provide data to support the above goals:

- Data Standards and Integration Workgroup (DSI-WG)
- Biomarkers and Clinical Endpoints Workgroup (BCE-WG)
- Preclinical and Clinical Sciences Workgroup (PCS-WG)
- Modeling & Simulation Workgroup (M&S-WG)
- Health Authorities Submissions Team (HAS)
- Integrated Sciences Team (IST)

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

Data Standards and Integration Workgroup (DSI-WG)

Mission

The DSI-WG provides the information technology (IT) infrastructure to support all CPTR data needs for developing regulatory science tools and methods to enable development of new TB drugs, drug regimens, and diagnostics. A key focus is aggregating all relevant data in a secure database for analysis by the CPTR workgroups and authorized researchers.

The DSI-WG addresses the requirements of gathering, assessing, standardizing, and pooling disparate sources of clinical and laboratory data into an integrated secure database. The Workgroup enables the efforts of the other Workgroups by determining their needs and priorities. This includes assisting in developing specifications for analysis datasets ('datamart specs') for the required data. The DSI-WG then works with member companies and partners to obtain information from the source data and to load it to secure C-Path data repositories. The DSI-WG describes the work needed to develop standards for remapping and integrating data from a variety of sources and formats using the current version of the CDISC SDTM TB Data Standard. It also addresses how the Consortium will integrate, submit, store, access, and analyze the data in the centralized system.

Goals

The DSI-WG addresses several primary goals: 1.) provide the infrastructure/architecture of the Information Technology and Data Management systems for the CPTR Consortium, 2.) develop CDISC TB data standards, and 3.) convert all data domains and individual data elements requested by the other Regulatory Science Consortium Workgroups to a standard usable format for population of the integrated database.

Deliverables

- TB Data Standards
  - Develop TB Data Standard v. 1.0 based on CDISC format.[2Q2012 - completed]
  - Update TB Data Standard v. 1.0 to include input from users of v. 1.0 and pediatric data elements. [4Q2014 – scope and planning discussions in progress]
• **CPTR Database**
  
  o Create a secure database repository for TB clinical trial and other research data. [2Q2012 - completed]

• **TB Data Acquisition & Mapping**
  
  o Facilitate the logistics for acquiring TB clinical trial and research data for the purposes of enabling critical CPTR projects, such as the development of clinical trial simulation tools for combination TB trials, upload to the database, and remap the data to the current TB Data Standard as needed. [ongoing, with several major data sets acquired and merging data sets expected]

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**Biomarkers & Clinical Endpoints Workgroup (BCE-WG)**

**Mission**

The BCE-WG identifies, develops consensus, and builds 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 regulatory review and qualification in a specific context of use when applicable.

**Goals**

There are a number of existing and emerging tools that would optimize development of new TB drug regimens; the BCE-WG will analyze various biomarker and clinical endpoints to help drive the development of new TB drugs and drug regimens. Ongoing and planned activities:

- **eData collection**—Exploring the use of e-data collection tools, such as patient reported outcome (PRO) assessments, for use in clinical trials and patient follow up. The sub-team is pursuing the utility of such an assessment to supplement where microbiologic data are missing to support robust review.

- **Molecular biomarkers**—Analyzing emerging molecular biomarkers for their use in developing new TB drugs and drug regimens, including use in industry and potential regulatory review and qualification. We acknowledge that such emerging markers will require sufficient clinical validation and the team seeks to develop pathways for such validation studies where needed.

- **Imaging biomarkers**—Analyzing emerging molecular biomarkers for their use in developing new TB drugs and drug regimens, including use in industry and potential regulatory review and qualification. We acknowledge that such emerging markers will require sufficient clinical validation and the team seeks to develop pathways for such validation studies where needed.

- **Liquid culture media**—Determine the utility of quantitative assessment of time-to-positivity assessment of liquid culture to inform phase II clinical trial design for TB combination studies. This team is currently pursuing evaluation of clinical trial data to support review via a pre-IND mechanism with FDA.

- **Other emerging technologies**—Identify and evaluate other emerging technologies for their use in developing new TB drug regimens.

**Deliverables**

• eData collection
o Complete the roster of subteam participants and schedule monthly telecons following the CPTR 2013 Workshop discussions. [4Q2013]

o Develop a detailed work plan for evaluating the use of e-data collection tool(s) (including their development and validation) and potential regulatory pathways. [1Q2014]

o Reach critical go/no-go decisions on e-data collection tool(s) and identify any related alternate approaches. [2Q2014]

- **Molecular Biomarkers**
  
o Complete the roster of subteam participants and schedule monthly telecons following the CPTR 2013 Workshop discussions. [4Q2013]
  
o Develop a detailed work plan with go/no-go decisions, including A.) evaluating current molecular markers, and B.) tracking and evaluating emerging molecular markers, C.) determining data availability, and D.) evaluating potential regulatory pathways. [1Q2014]
  
o Develop an inventory and preliminary evaluation of current molecular markers. [4Q2013]

- **Imaging Biomarkers**
  
o Complete the roster of subteam participants and schedule monthly telecons following the CPTR 2013 Workshop discussions. [4Q2013]
  
o Develop a detailed work plan with go/no-go decisions, including A.) evaluating current imaging biomarkers, and B.) tracking and evaluating emerging imaging molecular markers, C.) determining data availability, and D.) evaluating potential regulatory pathways. [1Q2014]
  
o Develop an inventory and preliminary evaluation of current imaging markers. [4Q2013]

- **Liquid Culture Media**
  
  - **Data Track**
    
o Complete data acquisition, remapping, and statistical work. [2Q2014]
    
o Complete and submit a ‘briefing book’ document with a thorough descriptive analysis of obtained data sources to FDA (pending final determination). [3Q2014]

  - **Scientific Track**
    
o Includes an analysis of REMOX and other data sources. [4Q2014]
    
o Finalize and submit liquid culture paper for publication. [4Q2014]

  - **Regulatory Track**
    
o Working through the Pre-IND process, submit analysis plan to FDA for review. [4Q2013]
    
o Work with the FDA through the Pre-IND process for further evaluating and analyzing liquid culture media for TB drug and drug regimen development; e.g., use in FDA guidance documents. [2Q2014]
    
o Complete regulatory review and determination. [2Q2015]

- **Other Emerging Technologies**
Survey the field for additional biomarker and clinical endpoint tools for enhancing TB drug and drug regimen development [1Q2014 and ongoing]

**Preclinical and Clinical Sciences Workgroup (PCS-WG)**

**Mission** The PCS-WG primarily develops 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, drug interaction potential and pharmaceutical profiles. These tools may be submitted to regulatory authorities for regulatory review and/or qualification as appropriate. The PCS-WG also addresses other issues as pharmaceutics, clinical PK/PD analyses of concentration vs. pharmacologic response data from clinical studies.

**Goals** The PCS-WG work to address specific topics including those outlined below:

- **Preclinical in vitro and in vivo models**—The most widely used preclinical efficacy models—different mouse and guinea pig models—have their strengths and weaknesses. There is therefore a great interest in the development of models with faster readouts and more human-like pathology. The PCS-WG will evaluate the evidence base and develop criteria for the utility of the various preclinical models to test new drug and drug regimen 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. The PCS-WG will work to support preclinical drug safety and toxicology studies for new TB drugs and drug regimens.

- **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, the PCS-WG will consider supporting additional in vitro and in vivo combination experiments. Also, approaches to predicting drug-drug interactions in humans, e.g., physiologically based (PB) PK methods, will be considered.

- **Preclinical and clinical PK/PD modeling & 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 bio-imaging 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 will be given to the optimal formulation approaches for the individual TB drug candidates, based on their pharmaceutical properties.

• **Preclinical and clinical sciences knowledge gaps**—The PCS-WG 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 CPTR project.

### Deliverables

- **Hollow Fiber Model System (HFS)**
  - Prepare an initial ‘briefing book’ and submit to FDA and EMA for regulatory review. [4Q2013]
  - Conduct in-person VXDS meeting with FDA to review the Administration’s input and regulatory pathway options. [4Q2013]
  - Develop a work plan to implement the chosen regulatory pathway(s) for FDA and EMA consideration of the HFS model. [to be determined]

### Modeling & Simulation Workgroup (M&S-WG)

**Mission** Working closely with the DSI-WG, the M&S-WG uses pooled data to create robust (in terms of scope and predictive accuracy) empirical, mechanistic, and systems biology models and quantitative simulation tools (Figure 6) to facilitate TB drug and drug regimen development.

**Goals** A number of critical weaknesses exist in the science of TB drug development. The M&S-WG will support a related set of work streams that directly or indirectly address some of the current limitations in TB combination drug development, including:

- **Empirical drug-disease-trial model**
- **PBPK modules on Simcyp platform**
- **In vitro Hollow Fiber System (HFS) model studies**
- **Population PK-PD in TB**
- **Mechanism-based systems pharmacology model for TB**
- **QT Assessment and Interpretation in TB Drug Development**

### Deliverables

- **Empirical Drug-Disease-Trial Model**
  This project will deliver an empirical trial simulation platform where colony forming units (CFU) and time-to-positivity (TTP) are the main endpoints of interest. The team will execute a two-stage approach:
Stage one will deliver a clear understanding of the strengths/weaknesses/data gaps of published TB models; this initial activity has been launched as part of the current grant. [1Q2014]

Stage two will result in an empirical drug-disease-trial model characterizing the time course of CFU & TTP as a function of regimen and patient type (DR, MDR, and XDR), accounting for trial components such as dropout rates. This drug-disease-trial model will be the basis for a clinical trial simulation tool for TB studies. Given the continuously evolving nature of modeling and simulation tools, this proposed model could be expanded as additional data are obtained. [2Q2014]

- **PBPK Modules on Simcyp Platform**
  - This model development project will produce PBPK models implemented on the Simcyp platform to map complex mechanistic drug distribution processes in the infected, inflamed, and damaged lung with the goal of improving treatment selection and regimens to optimize drug exposure across the heterogeneous sites of action. [1Q2014 version 1.0; 4Q2016 refinements]

- **In vitro Hollow Fiber System (HFS) Model Studies**
  - This work stream will characterize the predictive performance of the HFS model on clinical outcome, specifically time-to-eradication, potential for resistance emergence, synergistic combinations, and treatment regimen. The scope of the first stage of the proposed HFS effort will include filling data gaps identified by the ongoing HFS assessment for regulatory submission to FDA (planned for fall 2013) by the PCS-WG of CPTR. Upon completion of the 1st stage of this work stream and the assessed predictive utility of the HFS, a go/no go decision will be made regarding proceeding to the 2nd stage of the project. The 2nd stage of the HFS effort will include the evaluation of novel, untested regimens/combinations in the HF systems. Two independent laboratories will perform key studies to accelerate completion of the HFS experiments, assess inter-lab variability and compare the impact on HFS data assessment. [4Q2016]

- **Population PK-PD in TB**
  - This effort will mine the available PKPD data where therapeutic drug monitoring was practiced. This work will help to determine if dose adjustments of anti-TB therapy resulted in a difference in outcome. The work team will ensure that data will be collected and/or re-mapped to CDISC standards and included in the larger CPTR data repository. This effort will positively contribute to the empiric clinical trial simulation tool described above. [2Q2016]

- **Mechanism-Based Systems Pharmacology Model for TB**
  - This model development effort will enable a systems pharmacology approach to incorporate mechanism of action for multiple anti-TB agents, pharmacokinetic properties for those drugs, potential for synergy, resistance potential, and clinically relevant outcomes including CFU TTP. This work will also be informed by preclinical data and learnings from ongoing CPTR workgroup efforts, including the current liquid culture and lesion biomarker work,
data from the HFS system, the PBPK modeling effort, and the proposed empirical clinical trial simulation tool. [2Q2016]

- **QT Assessment and Interpretation in TB Drug Development**
  - QT prolongation has been observed with many of the drug therapies used to treat TB. However, the clinical risk/benefit and differentiation between TB combination regimens is unclear. The aims of this project are 1) to collate historic 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) to provide guidance/recommendations on suitable experimental designs (in vitro, preclinical, and clinical), data analytical approaches, signal interpretation, and go/no go decision-making related to QT prolongation in the context of new TB drug combination development. [3Q2015]

![Figure 6: Clinical disease-progression modeling](image)

**Health Authority Submissions Team (HAS)**

The HAS Team 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 HAS Team is responsible for:

- Seeing that the collation of such information is ready for submission to the health authorities.
- 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.

**Integrated Sciences Team (IST)**

**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 BCE-WG of the need for a biomarker and its likely context of use.
2. Alert the DSI-WG that new data elements will be needed for the new TB diagnostic biomarker.
3. Alert the HAS Team that a qualification request for the new diagnostic biomarker will be forthcoming.
4. The HAS Team 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.

**CPTR RAPID TB DRUG SUSCEPTIBILITY TESTING CONSORTIUM**

**Mission & Goals**

The goal of the CPTR Rapid TB Drug Susceptibility Testing Consortium (CPTR Rapid DST Consortium) is to accelerate the development of a WHO-qualified, clinically useful *in vitro* diagnostic assay for rapid drug susceptibility testing of TB to facilitate drug development and rational use of new drug regimens.

TB treatment protocols in much of the world are based on empiric first-line therapy for all patients. Recent studies have shown that drug resistant TB is more prevalent than previously recognized, and that many patients are receiving sub-optimal treatment with ineffective or partially effective drug regimens. Inadequate treatment is a driver of drug resistance and ongoing transmission of TB. Furthermore, direct transmission of multi-drug resistant (MDR) TB is now more common than was once thought.
The original TB Diagnostics Research Forum was convened in 2012 to communicate and collaborate to maximize resources to address DST issues related to new drugs and regimens. The CPTR initiative has been working since 2010 to accelerate the development of a novel drug combination for TB that is more efficacious, faster acting, and safer than current therapies. The two programs joined in 2013 to align on developing an accurate, cost effective DST assay with new TB drug combination(s) to ensure that all TB patients are initially treated with the best therapeutic option. Sharing research and clinical sample data relevant to understanding resistance profiles for existing and newly emerging TB drugs will be critical for achieving the mission of this consortium. Therefore, a supporting legal framework and commensurate protected database will be developed for to support this initiative.

**Workgroups**

Four workgroups are tasked with conducting the projects to fulfill the CPTR DST Consortium’s mission. These workgroups may be modified and other workgroups created as necessary.

- Enabling Sciences Workgroup (ENS-WG)
- Surveillance Workgroup (SVR-WG)
- Economic Assessment/Impact Modeling Workgroup (MOD-WG)
- Assay Development Workgroup (AYD-WG)

In addition, an Integrated Sciences Team (DST-IST) comprised of the workgroup co-chairs serves to coordinate and integrate the workgroups’ efforts to increase their effectiveness.

**Integrated Plan**

The CPTR Rapid DST workgroups’ missions, goals, and deliverables are highly interdependent. The following outlines key interdependencies and an integrated development plan for the DST Consortium.

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**Figure 7: Interdependencies among the Workgroups, the DST output, and its intended goal**

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**CRITICAL PATH TO TB DRUG REGIMENS INITIATIVE**
Two of the four workgroups, the Enabling Sciences Workgroup and Surveillance Workgroup, generate, collect, and assimilate relevant data to inform the other two workgroups. Frequent interactions among members of these two workgroups are required to prioritize and advance their work (Figure 7). The DST-IST, comprised of the workgroup co-chairs and supported by scientific and programmatic staff from C-Path and NIH, helps ensure that this is carried out efficiently.

The Economic Assessment & Modeling Workgroup uses the output from Enabling Sciences Workgroup and the Surveillance Workgroup to produce its deliverables. The Assay Development Workgroup uses the output from all the other workgroups to generate the target product profiles (TPPs), which is the Consortium’s main output. The TPPs will be presented to the WHO-STAG-TB for review and pre-qualification for the intended purposes and used by in-vitro diagnostics manufacturers that seek pre-developmental regulatory approval.

Integration of the Rapid DST Consortium with the Other CPTR Arms

The CPTR Rapid DST Consortium is coordinated closely with the other CPTR arms to achieve the initiative’s goals. The DST-IST meets periodically with the Regulatory Science Consortium / Research Resources Group -IST to ensure that all CPTR activity is fully informed and coordinated. A number of CPTR leaders serve on both the ISTs, which ensures that all major developments are shared rapidly. In addition, the CPTR quarterly workgroup report includes all four arms. This report provides a comprehensive update on all work streams and keeps all CPTR participants informed and helps optimize their efforts.

Enabling Sciences Workgroup (ENS-WG)

Mission  Discovery and validation of the molecular basis for resistance and correlation of resistance to clinical outcome.

Goals  There are a number of scientific obstacles to developing rapid DST for current and future drug regimen components; this workgroup will generate and analyze the molecular data to drive the development of molecular DST assays. Ongoing and planned activities include:

- Discover relevant drug resistant mutations for potential use in molecular assays
- Correlate genetic resistance mutations with phenotypic resistance and clinical outcomes
- Optimize phenotypic assays
- Develop platforms for sharing data
- Collaborate with drug developers to clarify/interpret molecular drug resistance profiles

Deliverables

The primary deliverables and target delivery dates for the Enabling Sciences Workgroup includes:

- Discover relevant drug resistance mutations for potential use in molecular assays. [initial report 2Q2014]
- Correlate genetic resistance mutations with phenotypic resistance and clinical outcomes. [TBD]
- Optimize phenotypic assays. [TBD]
- Develop platforms for sharing data. [3Q2013]
• Collaborate with drug developers to clarify/interpret molecular drug resistance profiles. [TBD]

Interdependencies
The Enabling Sciences Workgroup is dependent on the Surveillance Workgroup’s output, access to cutting edge original research data from drug developers and *in-vitro* diagnostics manufacturers, and on research efforts within academia, CDC, and others. A legal framework is required for these partners to provide and share access to vital data and other proprietary information.

Surveillance Workgroup (SVR-WG)

Mission To improve understanding of the magnitude and trends of drug resistances in high burden countries and globally, with particular focus on new and existing drugs for which resistance surveillance data are largely unavailable. Also to develop cost effective strategies for surveillance of TB drug resistance based on high-throughput molecular technologies.

Goals This workgroup will assist the production of surveillance data on resistance to new and selected existing drugs, align the Rapid DST Consortium’s efforts with the WHO drug resistance surveillance project, and validate high-throughput molecular methods for surveillance of drug resistance. Ongoing and planned activities include:

• Facilitate production of surveillance data on resistance to new and selected existing drugs.
• Align the Rapid DST Consortium’s efforts with the WHO drug resistance surveillance project and other relevant initiatives.
• Validate high-throughput molecular methods for surveillance of drug resistance.
• Lead efforts to partner with relevant organizations to develop standardized language for drug-resistant surveillance.

Deliverables
The primary deliverables and target delivery dates for the Surveillance Workgroup includes:

• Determine the global trends in the burden of resistant TB. [first report 1Q2014]
• Align the Rapid DST Consortium’s effort with the WHO drug resistant surveillance and other relevant initiatives. [3Q2013]
• Validate molecular methods for surveillance. [TBD]
• Facilitate the combined analysis of surveillance data for a better picture of global drug resistance. [4Q2014]

Interdependencies
The Surveillance Workgroup is primarily dependent on the Enabling Sciences Workgroup, requiring timely updates on new scientific discoveries in areas such as TB genomics, role of non-TB mycobacteria in co-infections, and discovery of new drug resistance markers. It is also dependent on receiving relevant data and analyses from current clinical studies, such as the WHO five-country surveillance project and data from animal model studies and clinical trials using new drug/ new combination regime.
Economic Assessment/Impact Modeling (MOD-WG)

Mission Develop models that will inform decisions needed to develop target product profiles and to inform policy about use of DST with anticipated TB drug regimens.

Goals The workgroup will develop a two-stage modeling approach that will address both developing and deploying a rapid DST. Ongoing and planned activities include:

Deliverables

The primary deliverables and target delivery dates for the Surveillance Workgroup includes:

- Develop a drug susceptibility test—Define population-level impact and cost-effectiveness trade-offs related to different DST assays based on speed, sensitivity/specificity, cost/price, and technical specifications. [2Q2014]
- Deploy a drug susceptibility test—Define population level impact and cost-effectiveness of different DST algorithms (e.g., treat without DST, test failure’s only, test target population, test everyone) as a function of baseline resistance and rate of emerging resistance. [TBD]

Interdependencies

The Economic Assessment/Impact Modeling Workgroup is dependent on all three other Rapid DST Consortium workgroups, requiring timely input of data and key priorities. In turn, this workgroup will provide its interim analyses to the other workgroups to help clarify options and priorities. This iterative process will ensure that the output from each workgroup is relevant and responsive to evolving circumstances in the world of TB drugs and diagnostics.

Assay Development Workgroup (AYD-WG)

Mission Facilitate developing rapid TB DST assays to meet target product profiles.

Goals This workgroup will coordinate with industry to develop commercial in vitro diagnostic assays for TB DST, meeting target product profile(s).

Deliverables

The primary deliverables and target delivery dates for the Assay Development Workgroup includes:

- Develop consensus TPP based on market analysis for rapid TB DST (dependent on ongoing work by Mahdukar Pai). [4Q2014]
- Assess NIPRO LPA for PZA. [TBD]
- Outline the scope of current drug companies’ and developers’ plans for resistance testing and assay development. [2Q2014]
- Facilitate communication and coordinate the evaluation of new methods for DST and novel molecular technologies. [3Q2013]

Interdependencies

The Assay Development Workgroup is interdependent with the other three Rapid DST Consortium workgroups, using their data and analyses and in turn providing input on what is required throughout
this iterative process. The Assay Development Workgroup is dependent on guidance from the DST-IST and input from in-vitro diagnostics and drug manufacturers, so that its efforts are relevant to evolving needs and concurrent developments. A legal framework, as mentioned above, is required for these partners to provide and share access to vital data and other proprietary information.

**CPTR RESEARCH RESOURCES GROUP**

**Mission & Goals**

The CPTR Research Resources Group works to increase the likelihood of successful innovative TB drug development by creating a framework and infrastructure to 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 has a multifaceted approach to create foster an environment for successful innovative TB drug development. The Research Resources Group collaborates with experts to address the challenges of building clinical trial and laboratory site capacity and quality; funding late stage clinical development of TB drugs; developing global regulatory pathways; providing access and appropriate use of novel TB drug regimens; and addressing the complexity of TB drug markets.

The Research Resources Group supports efforts that meet the following criteria:

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

**Workgroups**

The CPTR Research Resources Group workgroups 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.

**Clinical Trials Infrastructure Workgroup (CTI-WG)**

**Overview**

The Clinical Trials Infrastructure Workgroup (CTI-WG) identifies efficiencies across clinical trial sites and supports 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 be successful, training and coordination within 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, and needs and opportunities for clinical trial site capacity building.

Process

The CTI-WG consists of representatives 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 CTI-WG works with existing efforts to identify an approach that builds on that already underway by CDC, WHO, NIH, and others.

Global Regulatory Pathways Workgroup (GRP-WG)

Overview

The Global Regulatory Pathways Workgroup (GRP-WG) identifies efficiencies in the regulatory pathway to develop a novel regimen by fostering dialogue among key regulatory agencies, WHO, and NTPs. The Workgroup works to develop a pathway for regulatory approval that incentivizes regimen development. Regulators from countries or regions with high TB burden are included in this process.

Because of the nature of TB, the CPTR’s goal is to foster development, testing, and regulatory review of a novel regimen(s) containing multiple compounds. Defining regulatory pathways is necessary to accelerate this process.

Process

The GRP-WG identifies priority areas for engagement on regulatory efforts. They receive input from other CPTR workgroups, working closely with the Regulatory Science Consortium and Drugs Development Coalition. CTI-WG members include experts in developing regulatory strategies for their companies or organizations, representatives of regulatory agencies, and other relevant experts on regulatory affairs.

Stakeholder and Community Engagement Workgroup (SCE-WG)

Overview

The Stakeholder and Community Engagement Workgroup (SCE-WG) facilitates 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

SCE-WG members 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 consist of experts in stakeholder and community engagement.

**Access and Appropriate Use of New Drugs (AAU-WG)**

**Overview**

The Access and Appropriate Use Workgroup (AAU-WG) identifies areas of missing evidence or expertise that may become a barrier on the critical path to the launch plan. This workgroup also helps to address questions of access or availability to drugs while they are in development. The AAU-WG also establishes a framework for dissemination and appropriate use once a new regimen(s) is approved and marketed.

While a new TB drug regimen is being developed, it is important to develop a strong evidence base and criteria to support access and appropriate use for when the regimen(s) is approved and ready for use.

**Process**

The AAU-WG works with the CPTR Drugs Development 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. AAU-WG members 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.

**CPTR DRUGS DEVELOPMENT COALITION**

The CPTR Drugs Coalition provides the framework for 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 Development Coalition, through which TB drug sponsors can make informed decisions concerning the regimens in which they wish to participate.

The CPTR Drugs Development 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 Drugs Development 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.