DRAFT

FAST-TB

Facilitating Accelerated Science and Translation for TB Regimen Development

FAST-TB

Tuberculosis (TB) is a global health crisis. An estimated 10.6 million people developed TB disease in 2021, and 1.6 million died of it. Combating this epidemic requires the development of effective anti-TB regimens.

With an increasing number of new chemical entities expected to transition into clinical testing in the next 5 years, high quality clinical trials are necessary to identify shorter, safer, and more efficacious regimens for TB treatment.

Development of new TB drugs and regimens is complex, lengthy, costly, and fraught with many obstacles and uncertainties. The therapeutics research community must establish rational approaches to identify the best drug combinations and develop novel trial designs to advance clinical development.

Development of new TB regimens should be based on evolving knowledge of the pharmacokinetic/pharmacodynamic (PK/PD) and microbial characteristics of the drugs, informed by novel biomarkers that can predict treatment response to accelerate and TB treatment trials.

Given the long duration and high costs of clinical development, and limited funding for TB research and development (R&D), it is crucial to streamline processes for the development of new TB treatments while addressing gaps and avoiding duplication of efforts.

This global health crisis requires a systematic and globalized approach to ensure that best practices and research designs are used to accelerate development of new TB regimens that can be procured and delivered efficiently to all those in needs.

Through creative approaches in translation science, FAST-TB will foster a more efficient and streamlined process for the development, evaluation and introduction of novel treatment regimens.

Goal and Objectives

Goal

The goal of FAST-TB is *to accelerate the development and implementation of novel TB regimens through supporting more efficient communication, coordination, and collaboration among key stakeholders and research groups throughout the treatment development and implementation pathway.*

FAST-TB will serve as a *platform* for promoting global collaboration and sharing of preclinical and clinical knowledge among clinical trial networks, funders, and other stakeholders to facilitate integrated approaches to R&D.

Objectives

FAST-TB will establish a coordinated global framework to accelerate the development of new TB treatments with the following objectives:

1. Support sharing of preclinical and clinical knowledge and data to accelerate progress of suitable regimens along the clinical development pathway.
2. Support and facilitate research to develop and validate biomarkers to advance development of new TB treatments.
3. Support and facilitate research to better understand factors associated with drug resistance and development of easily implementable assays for drug susceptibility testing along drug development.
4. Support and facilitate a research strategy for optimal introduction of new TB regimens in high burden countries that is informed by a nuanced understanding of real-world needs and a fostered engagement with relevant stakeholders.

FAST-TB will shape a globally coordinated approach to TB Therapeutic Development by serving as a platform to link organizations working at different points along the TB drug regimen development pathway.

Functional structure

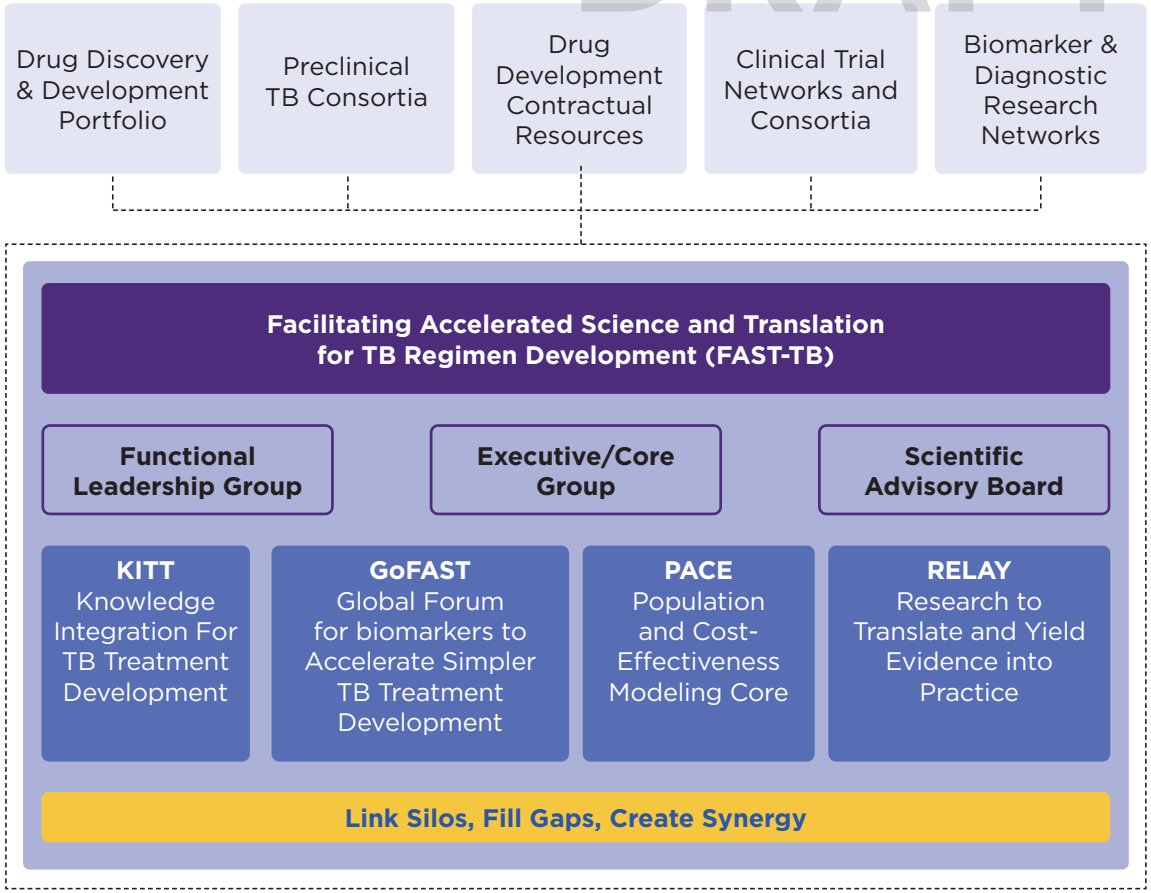
FAST-TB is supported by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) in partnership with CRDF Global, and operates through the following main Tracks:

1. **Knowledge Integration for TB Treatment Development (KITT)**
2. **Global Forum for evaluation of biomarkers to Accelerate Simpler TB Treatment development (GoFAST)**
3. **Population and Cost-Effectiveness Modeling Core (PACE)**
4. **Research to Translate and Yield Evidence into Practice (RELAY)**

A Global Partnership

FAST-TB aims to connect and link international and national stakeholders to ensure accelerated research leading to optimal treatment of all people affected with TB.

FAST-TB Leadership Structure



FAST-TB will connect and gap-fill existing NIAID and other global resources, networks, and projects to accelerate research translation along the treatment development pathway.

1: Knowledge Integration for TB Treatment Development (KITT)

Rationale

The current pipeline of new TB drugs has more potential now than it ever had over the last fifty years. Several international consortia are undertaking a new wave of clinical trials investigating various drug combinations including new compounds for TB treatment. The increased number and complexity of TB clinical trials requires better mechanisms for optimal sharing of knowledge, best practices, and advancements in trial designs to enable and maximize scientific knowledge, gains and benefits for clinical trial participants and investigators.

Goal

The overall goal of KITT is to accelerate TB drug and regimen development through synergizing global efforts and reducing duplication and competition for scarce resources. KITT aims to create an inclusive, collaborative framework for relevant consortia and groups involved in TB treatment R&D to share trial plans, designs, information and data to advance research outcomes.

Expected Outcome

KITT members will establish a global community of TB drug trialists to enable sharing of ideas and plans, and to build trust for the sharing of more sensitive information, when appropriate, during ad-hoc tracks collaboration. Through early sharing of knowledge, KITT will stimulate the creation of model-informed drug development frameworks for the generation of new knowledge-based TB treatments.

2. Global Forum for evaluation of biomarkers to Accelerate Simpler TB Treatment development (GoFAST)

Rationale

Rapid diagnosis and treatment are essential for effective TB care and management and for reducing the risk of emerging drug-resistant forms of TB, for which treatment options are more limited, burdensome, and costly. One of the most critical challenges in TB treatment development is the identification of reliable biomarkers to quantitatively assess the sterilizing capacity of new drugs and drug combinations and predict long-term treatment effects better and faster than current culture-based methods. The identification, validation, and integration of drug resistance biomarkers into existing diagnostic platforms would enable prompt adjustment of treatment regimens to improve patient outcomes and reduce the emergence of drug resistance, which is essential to preserve new TB drugs and regimens.

Goals and Objectives

The overall goals of GoFAST are to:

1. Advance the discovery, development, and validation of biomarkers to accelerate the development of new TB drugs and regimens and inform their clinical use, including among persons living with HIV.
2. Support and facilitate research to better understand mechanisms of resistance to new and existing TB drugs.
3. Advance the development of more efficient and cost-effective drug susceptibility assays that can be deployed at the POC and developed in alignment with ongoing clinical evaluations.

Expected Outcome

GoFAST will support and facilitate collaborations with leading TB researchers and key stakeholders to promote the development of novel biomarkers so as to facilitate decisions for advancing novel regimens to Phase 3 trials, facilitate early detection of drug resistance, and improve monitoring of TB patients on therapy. Such biomarkers should be easy to interpret and portable across clinical phases and should provide data to inform rank ordering and prioritization of regimens for clinical evaluation. Through this effort, FAST-TB aims to develop a strategy for the integration of biomarker assessment in clinical trials.

3. Population and Cost-Effectiveness Modeling Core (PACE)

Rationale

Computational and mathematical modelling approaches have advanced efforts to end TB through generating evidence-based data to inform research prioritization and public health decision-making. Thus, modelling has been used to estimate the health impact of new vaccines, drugs, diagnostics, and their combinations. While these models were based on the best available estimates at the time, they relied on now out-of-date assumptions on TB natural history and intervention characteristics, resulting in inaccurate estimates of their impact. In addition, they did not estimate cost-effectiveness and budgetary impact, which are critical for decision-makers. Modelling studies have advanced considerably over the last fifteen years, allowing adjustment of assumptions and simulations for generation of more refined estimates.

Goal and Objectives

The goal of PACE is to develop dynamic population and cost-effectiveness models to better understand and predict the impact of various interventions including novel treatment regimens, diagnostic strategies, and prevention modalities based on modern data, to systematically investigate their impact on global TB burden, including populations affected by HIV.

The specific objectives of PACE are to:

1. Update high-level estimates from classic papers using cutting edge TB natural history data to estimate the relative impact and cost-effectiveness of new TB directed interventions, and their optimal combination.
2. Estimate the public health impact and cost-effectiveness of novel short course treatment regimens and provide a menu of outcomes to inform decision-making.
3. Prioritize research goals for greatest public health impact and address modelling needs across FAST-TB.

Expected Outcome

PACE aims to collate and analyze the latest natural history data and apply state-of-the-art mathematical models to estimate the relative impact and cost-effectiveness of new interventions and their optimal combinations. FAST-TB partners and stakeholders will use the generated data and estimates in their evidence-based decision making, particularly for new TB treatments. Findings will be disseminated to ensure rapid actions at the global and country level.

4. Research to Translate and Yield Evidence into Practice (RELAY)

Rationale

The process of translating trial findings into clinical applications is complicated by potential limitations in evidence from various trials and a complex path through regulatory and normative approvals. In view of recent developments, the likelihood of introducing novel TB treatments has substantially increased. To effectively translate new regimens into clinical benefit, research studies should fulfill the needs of national programs and extend their benefits to special populations (e.g. children, pregnant women, people living with HIV) while meeting regulatory and normative requirements. This requires improved communication and collaboration among the many stakeholders engaged in translational research worldwide to overcome challenges and foster a harmonized approach across the research and development pathway.

Goal and Objectives

The goal of RELAY is to facilitate a research strategy that is informed by a nuanced understanding of real-world needs. To achieve this, RELAY will foster engagement with regulatory and affected communities and normative bodies as well as those responsible for the introduction of new TB regimens to ensure that research groups working upstream are cognizant of their needs and priorities.

The specific objectives of RELAY are:

1. To engage with international stakeholders and communities affected by TB to understand their perspectives and provide the appropriate channel(s) for community input into research prioritization and design;
2. To identify research priorities that can best inform the introduction of new TB regimens, taking into consideration the needs of end-users in high TB-burden countries;
3. To serve as a communication platform that enhances interaction among stakeholders involved in clinical research for TB treatment to refine research strategy and ensure that they are aligned with the broader community's expectations while minimizing gaps.

Expected Outcome

This effort will foster closer engagement of groups working along the treatment R&D pathway with groups responsible for introducing new TB regimens in care and practice. This includes regulatory bodies to hasten TB drug approvals through streamlined development and accelerated regulatory pathways. In partnership with the research community, key normative institutions, and those who benefit from this work, RELAY will help prioritize clinical research that aligns with the global realities of TB care and accelerate the introduction of more effective regimens that dramatically improve outcomes for TB patients.

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