

# SUPPORTING, MOBILIZING, AND ACCELERATING RESEARCH FOR TUBERCULOSIS ELIMINATION



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Accelerating Research for  
Tuberculosis Elimination



## SMART4TB

The Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination (SMART4TB) Consortium brings together experts in TB tools development, implementation science, capacity strengthening, civil society engagement, and policy guidance, with a plan to collaborate to transform TB control in the next five years. SMART4TB's strategy involves targeted research in collaboration with local partners in priority countries, strengthening capacity for conducting future research by country partners, and ensuring that the knowledge derived from research studies is translated into policy and practice at the global, national, and local level. The consortium, led by Johns Hopkins University (JHU), includes the University of California, San Francisco (UCSF), KNCV Tuberculosis Foundation (KNCV), the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), the Treatment Action Group (TAG) and regional collaboratives strategically based at research institutions in high-burden countries.

## Technical Area 2: Therapeutics

Despite significant advances towards shorter and safer TB treatment regimens, considerable knowledge gaps remain for the treatment of all forms of TB. Pregnant women and children continue to be treated with longer, more toxic, less acceptable, and sometimes less effective treatment regimens resulting in excess physical, psychosocial, and economic burden. World Health Organization (WHO) DR-TB treatment and prevention recommendations are largely based on 'very low quality of evidence' and are undercut by emerging drug resistance in many countries. There are three key limitations of previous TB clinical trials. First, children and pregnant women are not adequately included. Second, TB clinical trials are often rigidly designed to address regulatory requirements and neglect the broader uptake, acceptability, and economic issues needed to establish WHO guidelines, leading to challenges in implementation. Third, TB clinical trials are often cumbersome and time-consuming in the face of rapid changes in treatment approaches, such that results have diminished impact at trial completion. As a result, many guidelines are based on observational data, subject to considerable bias, and consequently, weaken global uptake.

## Therapeutics Objectives

In Year 1, Technical Area 2 (TA2) plans to develop novel regimen studies for drug-resistant TB and childhood TB, and rapidly assess the landscape of options for pregnant women in TB therapeutics clinical trials through the following technical objectives:

- Develop a randomized controlled trial to improve the treatment of rifampin-resistant TB by identifying both the right regimen and right duration, which depends on a patient's own baseline risk of treatment failure and relapse (PRISM-TB);

- Develop a trial protocol and begin site development for a treatment-shortening drug-susceptible TB treatment trial in children with a stratified medicine approach (SMILE-TB);
- Develop a consensus statement on TB therapeutic research in pregnant women (BRIDGE-UP); and
- Develop a protocol evaluating bedaquiline for TB prevention in adults, children, and pregnant women (BREAK-TB).

## Therapeutics Activities

TA2 Studies	Adults	Children	Pregnant Persons
DS-TB		SMILE-TB	BRIDGE-UP will identify consensus around DS-TB regimen to be studied in pregnant persons (HPMZ?)
RR-TB	PRISM-TB	PRISM-TB substudy will assess safety, tolerability, acceptability, cost and access to BDLL/C in children with RR-TB.	PRISM-TB substudy will assess PK and safety of BPaLM in pregnant persons
TB Prevention (DS-TB and DR-TB)	BREAK TB will assess BDQ for TB prevention among adults, children and pregnant persons with DS-TB and/or RR-TB exposure.		

**PRISM-TB:** PRISM-TB is a randomized controlled trial to improve the treatment of rifampin-resistant TB by identifying both the right regimen and duration, which depends on a patient's own baseline risk of treatment failure and relapse. The trial will enroll adolescents and adults with confirmed rifampin-resistant TB, based on a GeneXpert result, where they will be randomized to receive either the standard of care control strategy or an intervention strategy. The standard of care will be defined by WHO guidelines, which currently recommend six months of BPaLM. The intervention strategy will include one or two regimens given at different durations based on a participant's baseline risk of poor TB outcome.



**SMILE-TB:** SMILE-TB will be a treatment-shortening, noninferiority trial of children with presumed drug-susceptible tuberculosis where duration of therapy will depend on the participant's baseline risk of treatment failure or relapse. The trial will enroll children < 15 years with presumed drug-susceptible, including both microbiologically confirmed and clinically diagnosed tuberculosis (adjudicated as confirmed, unconfirmed or unlikely by an independent committee). Children will be randomized to receive either the standard of care (e.g., 2HPMZ/2HPM) or the intervention (e.g., 2HPMZ). If HPMZ is chosen as the study regimen, modeled rifapentine doses will be used and confirmed in a pharmacokinetic sub-study in the first enrolled participants.



**BRIDGE-UP:** BRIDGE-UP will explore the feasibility of evaluating specific drug-susceptible and drug-resistant regimens in pregnant women from both the perspective of maternal and infant safety and trial feasibility. The preliminary activities will include a systematic review of drug sensitive and drug-resistant TB drug and regimen candidates (e.g., RPT, MFX, Pa, BDQ, PZA, etc.) during all stages of pregnancy and lactation. This will be followed by a workshop to determine consensus on proposed research questions for drug-susceptible and drug resistant tuberculosis regimens to be evaluated in pregnant women (e.g., HPMZ, BPaLM, etc.), yielding a report summarizing consensus on proposed research questions including DS and DR-TB regimens to be evaluated in pregnant women.

**BREAK-TB:** This study concept for a randomized controlled trial to define the efficacy of bedaquiline for tuberculosis prevention will be explored in Year 1. The trial will enroll adults, children, and pregnant persons with an indication for TB prevention including latent infection and/or age < 5 years with known drug-susceptible or rifampin-resistant tuberculosis exposure. Participants would be randomized to receive either four weeks of bedaquiline or the standard of care for DS-TB or RR-TB contacts, which may be informed by the V-QUIN and TB-CHAMP trials within the next six months.