SMART4TB

Richard E. Chaisson, MD
Johns Hopkins University Center for TB Research

Supporting, Mobilizing, and Accelerating Research for TB Elimination

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Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

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USAID Cooperative Agreement to accelerate progress to achieve the End TB goals in high-burden countries

UCSF

Johns Hopkins University

KNCV Tuberculosis Foundation

Elizabeth Glaser Pediatric AIDS Foundation

TAG Treatment Action Group

Regional Collaborative Hosts

walimu

KTMA

PHRU Improving Life Through Research

Perinatal HIV Research Unit of the University of the Witwatersrand

Y.R.G. CARE

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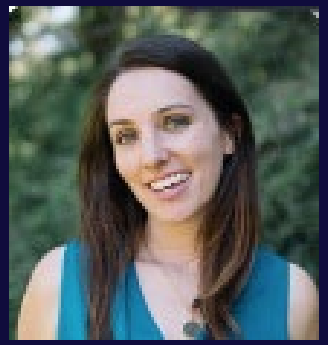
Gillman School of Public Health

SMART4TB Leadership

Richard Chaisson
Johns Hopkins University



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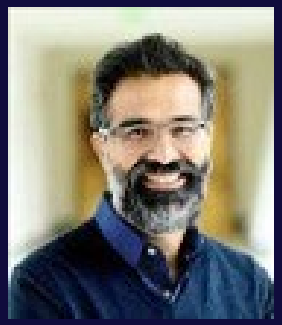

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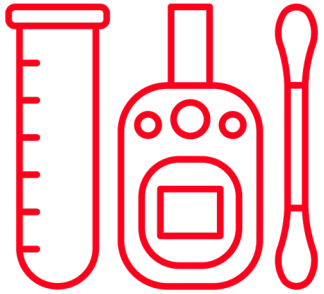
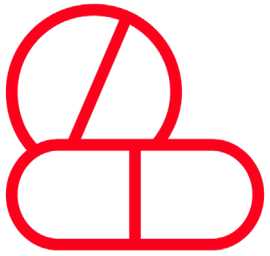
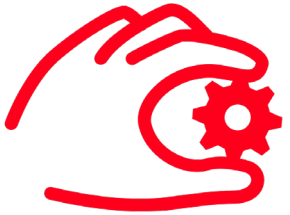
Technical Areas



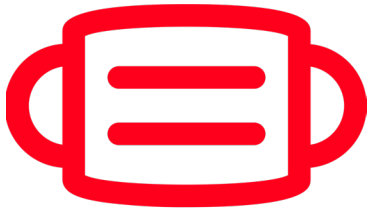
TA1: Diagnostics



TA2: Therapeutics



TA3: Operational Research



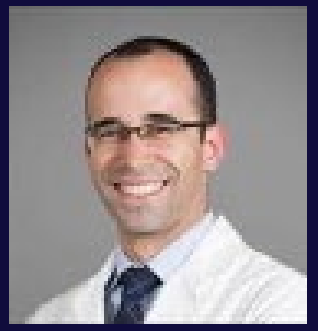
TA4: Interrupting Transmission

TA5: Vaccine Preparedness

TA6: Capacity Strengthening

TA7: Policy Translation

Technical Area 2: Therapeutics



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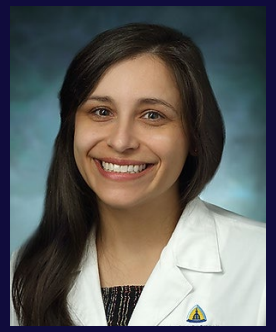

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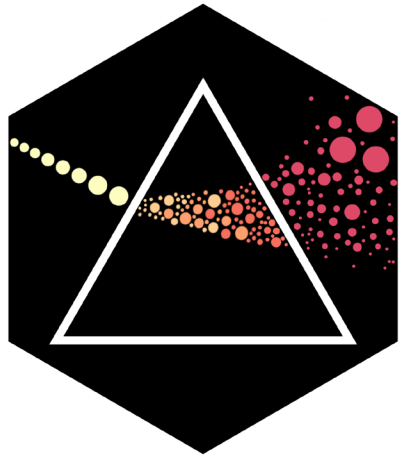
TA2: Therapeutics

Key activities and deliverables: Develop novel regimen trials for DS- and DR- TB, and rapidly assess the landscape of options for pregnant women and children in TB therapeutics trials:

- PRISM-TB: Randomized trial in adults and children to improve the treatment of DR-TB by optimizing regimens and duration using baseline predictors for treatment failure and relapse
- PRISM-Kids: Observational study of risk-based stratification of DR-TB treatment in children
- SMILE-TB: Randomized trial of a treatment-shortening DS-TB treatment trial in children with a 2-month regimen
- BREACH-TB: Develop a protocol evaluating bedaquiline for TB prevention in adults, children, and pregnant women with and without HIV
- BRIDGE UP: A consensus conference on TB therapeutic research in pregnant women, October 2023

Activity 2.1 - PRISM-TB



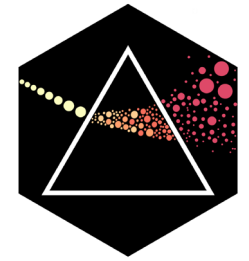
Program for RIfampicin-resistant disease with Stratified Medicine for TB (PRISM-TB)

An open-label, randomized, controlled, Phase 3 clinical trial for the treatment of rifampicin-resistant TB

PRISM-TB Overview

- **Design:** International, multicenter, randomized, controlled, open-label, three-arm, pragmatic, stratified medicine, treatment shortening, noninferiority Phase 3 clinical trial.
- **Population:** Adults and adolescents aged ≥14 years with confirmed rifampicin-resistant pulmonary tuberculosis.
- **Stratification:** Randomization will be stratified by risk strata and site.
- **Study duration:** 104 weeks.
- **Sample size:** Total sample size is 690 participants (230 per arm) with FQ-S MDR/RR-TB, and 150 participants (150 single arm) with FQ-R MDR/RR-TB.
- **Pharmacokinetics:** Sparse PK sampling in all participants, and intensive PK sampling in 10% of participants in experimental arms.

PRISM-TB



Randomization of regimens (1:1:1)

Control

‘Preferred’ WHO Control (26-39w)

Intervention

Stratification

Duration

Eligible persons with FQ-S RR-TB (N=690)

- BPaLM → 17w
- BPaLM
  - **Harder-to-treat TB** → 26w
  - **Easier-to-treat TB** → 13w

Eligible persons with FQ-R RR-TB (N=150)

- BPaL
  - **Harder-to-treat TB** → 39w
  - **Easier-to-treat TB** → 26w

All participants followed up to 18 months post-randomization

Assuming approximately 75% easier-to-treat TB, 25% harder-to-treat TB

B – Bedaquiline
Pa – Pretomanid
L – Linezolid
M – Moxifloxacin

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PRISM-TB Pregnancy and Lactation

Focus on pregnancy and lactation

- Focus on pregnancy, lactation
  - Pregnancy at enrollment: Plan to receive BPaLM in experimental arms
  - Pregnancy after enrollment: Plan to reconsent to continue study-allocated regimen (including BPaLM)
  - Lactation: Reconsent to continue study-allocated regimen

PRISM-TB Kids

Treatment-shortening Phase IIc Trial

Open-label, **nonrandomized**, non-comparative prospective observational study

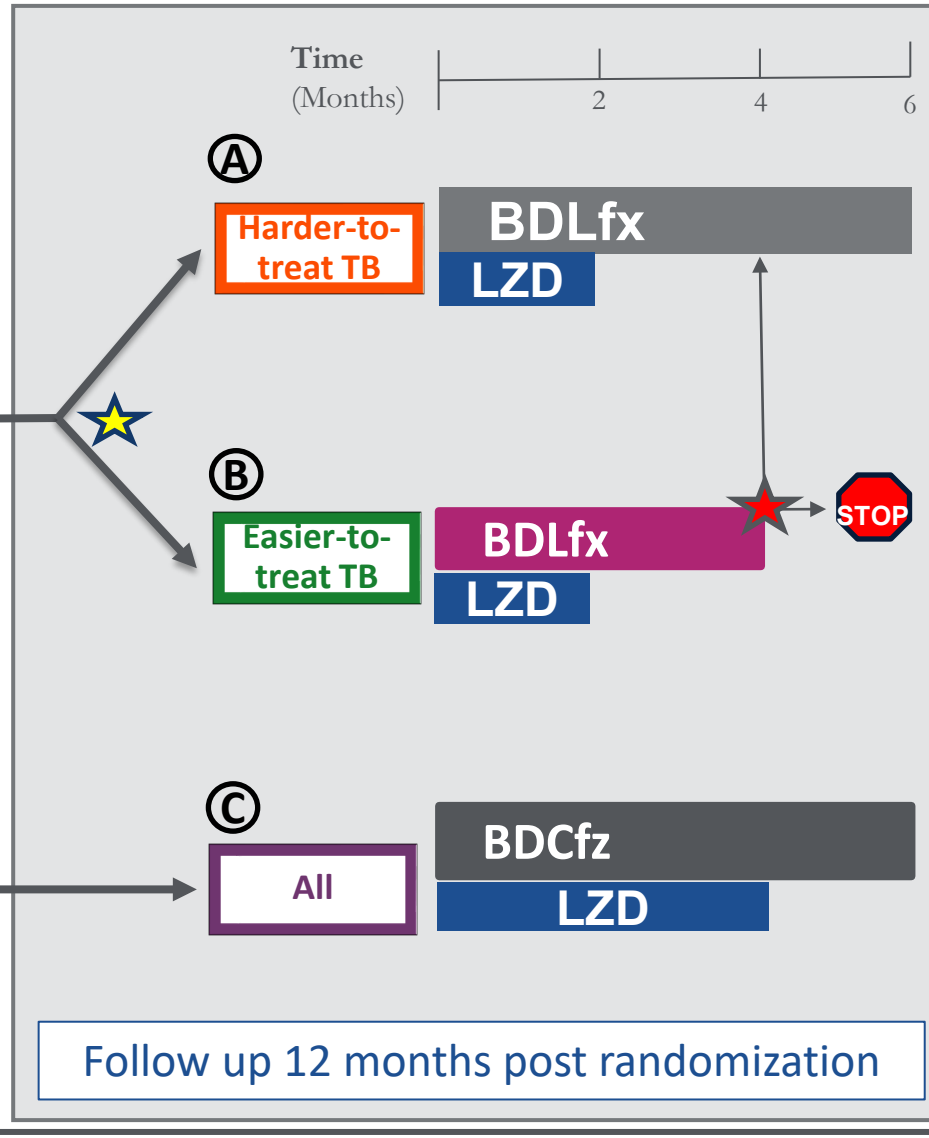
(Total N~100)

Children < 14 years with presumed RR-TB, FQ susc or unknown

= stratification algorithm*

= EOT assessment +/- extension

Children < 14 years with presumed RR-TB, FQ resistance



Late Detections: Ppts in Groups A or B who are discovered after treatment assignment to have FQ-R will switch to Group C, with start of 6-mo treatment defined as time of switch to BDC

Follow up 12 months post randomization

B Bedaquiline
D Delamanid
Lzd Linezolid
Lfx Levofloxacin
Cfx. Clofazimine

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SMILE-TB

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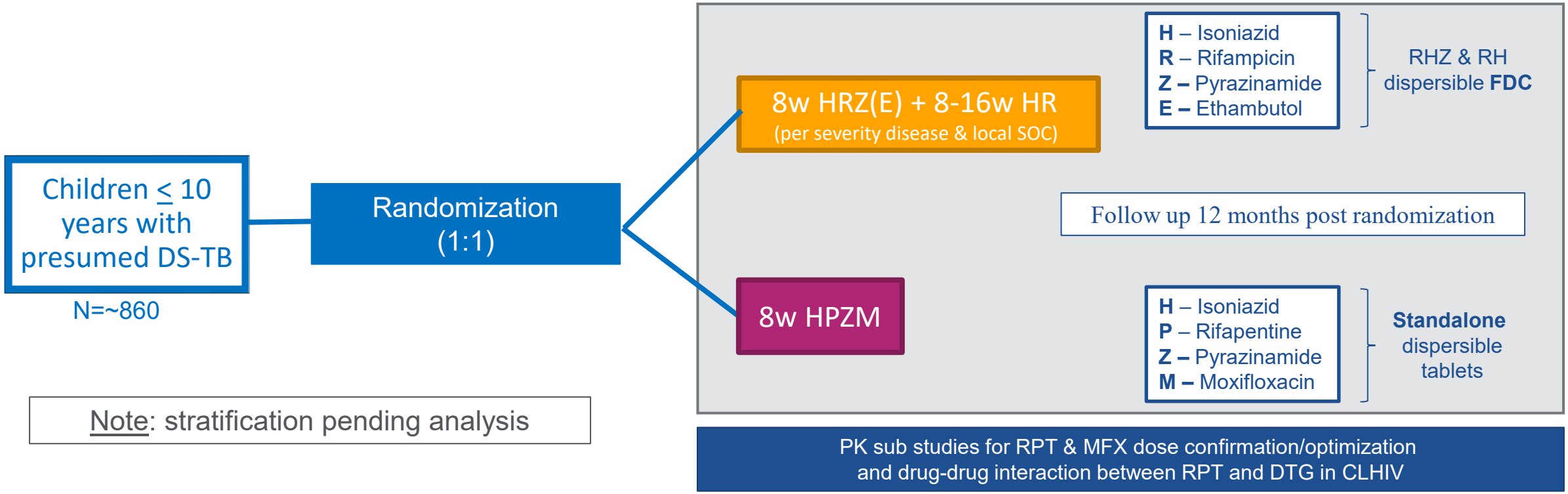
SMILE-TB

Stratified **M**edic**I**ne for Drug-susceptib**LE TB** in Children (SMILE-TB)

Open-label, Randomized, Controlled, Treatment-shortening Noninferiority Trial



SMILE-TB – Objectives

Primary Objectives

- To determine if a 2-month HPMZ regimen in children with presumed drug-susceptible TB disease is **non-inferior** to 4-6 months of HRZ(E), as per the standard of care in children with and without HIV
- To determine the **weight-banded dosing of RPT** taken as part of the HPMZ regimen
- To evaluate the **pharmacokinetics of DTG** among children with HIV taking the HPMZ regimen

Key Secondary Objectives

- To characterize factors correlated with unfavorable treatment outcomes to assess a stratified treatment algorithm for participants with high risk of unfavorable outcome at baseline who may require longer durations of therapy
- Safety, tolerability, adherence, palatability, acceptability, cost & cost effectiveness
- PK/dosing in malnourished children

BREACH-TB

(**B**edaquiline **R**oll-out **E**vidence in **C**ontacts and People Living with **H**IV to prevent **TB**)

An open-label, randomized, controlled, Phase 3 clinical trial of bedaquiline for prevention of TB disease in PLHIV and contacts of drug-susceptible and rifampin-resistant TB

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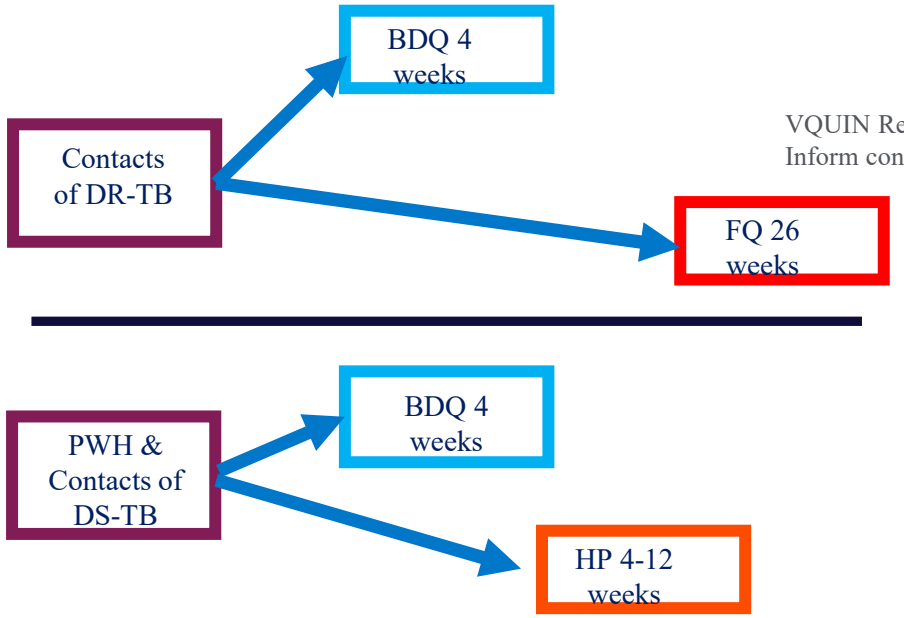
Fighting for an AIDS-free generation

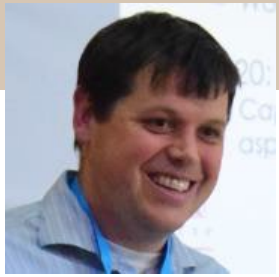
BREACH-TB: Study schema

- Phase 3, open-label, multicenter, randomized, controlled trial
- Two Primary Arms
  - Adults & children who are close contacts of RR-TB
  - People with HIV and Adults & Children who are close contacts of DS-TB
- Non-inferiority design comparing efficacy & safety of BDQ* vs. SOC
- Follow-up to 24 months post-randomization
- Expected sample size: 800-1000 per indication (DS/PWH vs. RR-TB)



All participants followed up to 24 months post-randomization

BREACH-TB: Variables for preliminary sample size estimation



Patrick Phillips, UCSF

Using Averted Event Ratio (AER)

1. Untreated/placebo event rate
   - LTBI trial assumptions (over ~2y): 1.3-1.5/100py (4R, VQUIN), 2.5/100py (TBTC 26/37, Phoenix)
   - HHCs high risk (TBI+, PWH, children <5): 2.7/100py (1.4 confirmed/prob) over 1y[1]; all HHCs: 1.3-1.1/100py over 1-2y[1,3]
   - HHCs <5 yrs: 7.0/100py over 1y (incl. possible TB)[1,4]; 3.8/100py over 2y[2]
   - PLWH: 6.8/100py (~4.2 confirmed/prob) over 1y in HHCs[1]; over ~2y: 2.5/100py in TEMPRANO w/o IPT, 3.6/100py Rangaka, ~2.1/100py Thrio
2. Effectiveness of control arms (70%-90%, pending VQUIN trial results)
3. Effectiveness of BDQ arm (assumed to be same as control, as is standard in non-inferiority trials)
4. Margin of non-inferiority on AER (assumed to be 50%, c/w FDA guidance)
5. Loss to follow-up (10%)
6. Power (explore both 80% and 90%)
7. Significance level, one-sided 2.5% (= two-sided 5%).

1. Krishnan, 2. Martinez, 3. Fox, 4. Marais

BRIDGE-UP
Pregnancy Consensus Project

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Pregnancy Consensus Roadmap

4-day meeting co-convened by USASID, SMART4TB, WHO, and IMPAACT Network

- Stakeholders:
  - Researchers, Ethicists, Regulators, Industry, Funders
  - WHO, Stop TB Partnership
  - Affected Community
- Focus: protect pregnant women *through* research, not *from* research
- Ethical principles, Key trial design principles, Pharmacovigilance/Surveillance
- Community perspective
- Working groups for Preclinical Issues and Clinical/Trial Issues

SMART4TB is made possible by the generous support of the American people through the United States Agency for International Development (USAID) and is implemented under cooperative agreement number 7200AA20CA00005. The consortium is managed by prime recipient, Johns Hopkins University.

Thank you!

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