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PRISM-TB Trial: Personalized Regimens to Improve Safety & cure in Multidrug-Resistant TB

PRISM-TB Trial Aims to Optimize Treatment for Drug-Resistant TB with Personalized Approach

- **Problem:** DR-TB treatment remains long, toxic, and one-size-fits-all, with 40-50% global success rates
- **Gap:** Limited evidence on tailoring regimens using clinical, microbiological, and pharmacologic factors
- **Innovation:** PRISM-TB tests a personalized algorithm to optimize duration, drug selection, and dosing
- **Objective:** Improve cure rates, reduce toxicity, and shorten treatment for DR-TB

Why Personalization for DR-TB?

- **Heterogeneity:** Patients differ in disease severity, resistance patterns, drug exposure, and comorbidities
- **Toxicity burden:** Standard regimens cause hearing loss, neuropathy, QT prolongation in >30%
- **Hypothesis:** A precision-guided approach using baseline biomarkers + therapeutic drug monitoring will achieve ≥80% cure with ≤6 months treatment and <15% Grade 3+ toxicity vs. standard of care

Trial Design

- **Design:** Multicenter, open-label, randomized 1:1
- **Population:** n=300 adults with RR/MDR-TB, HIV+/-
- Arms:
  -Standard of Care: 6-month BPaL/M regimen per WHO
  -PRISM Arm: Personalized regimen guided by algorithm
- **Sites:** South Africa, India, Peru – high DR-TB burden settings
- **Duration:** 24-month enrollment + 12-month follow-up

Personalization Algorithm : How We Tailor Treatment

- **Baseline inputs:** Xpert XDR results, chest X-ray severity score, BMI, HIV status, QTc, creatinine

- **Week 2 TDM:** Linezolid, bedaquiline, pretomanid levels to adjust doses

- **Decision rules:**
- **De-escalate:** Low burden + good drug exposure → 4-month regimen
- **Intensify:** Cavitary disease + low exposure → add clofazimine/extend to 9 months
- **Substitute:** QTc >450ms → replace bedaquiline with delamanid

- **Monitoring:** Monthly sputum culture, ECG, audiometry, symptom-directed toxicity checks

Primary & Key Secondary Endpoints: Measuring Success

- **Primary:** Favorable outcome at 12 months – cure + treatment completion without relapse

- **Key Secondary:**
- Time to culture conversion
- Grade 3-4 adverse events, esp. neuropathy, myelosuppression, QTc prolongation
- Patient-reported quality of life – TB-specific PRO tool
- Cost per successful outcome

- **Analysis:** Non-inferiority for efficacy, superiority for safety/tolerability

Preliminary Data & Safety: Early Results from n=120 Interim Analysis

- Enrollment: 67% male, 38% HIV+, 22% with fluoroquinolone resistance
- Culture conversion: Median 4 weeks PRISM vs 6 weeks SOC
- Safety: Linezolid dose reductions in 45% PRISM arm, with 60% less Grade 3 neuropathy vs SOC
- DSMB review: No safety concerns; adaptive algorithm functioning as intended
- Adherence: 94% in PRISM arm due to reduced pill burden and fewer side effects

Significance & Innovation: Why PRISM-TB Matters

- **Clinical impact:** First trial to prospectively test individualized DR-TB duration and dosing
- **Equity:** Brings precision medicine to underserved, high-burden communities
- **Programmatic:** Algorithm designed for use in routine clinics with point-of-care tools
- **Policy:** Evidence to inform next WHO DR-TB guidelines on stratified carePatient-centered: Aligns treatment with person's disease, body, and life

Next Steps & Acknowledgements: Path to Implementation

- **Complete enrollment:** Q4 2026; primary results Q2 2028
- **Implementation study:** Test PRISM algorithm in NTPs if successful
- **Tools:** Developing open-access app for clinicians to use algorithm
- Acknowledgements: Funders, trial sites, community advisory boards, and participants

Thank you – Questions?