# RCT Transition Plan: From Ecological Findings to Pilot and Randomized Controlled Trials

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This document outlines the pathway to move from ecological and cohort findings to pilot interventional studies and definitive RCTs for microbiome-informed therapies in T2DM and TB.

## 1. Rationale for RCTs

Ecological and cohort analyses identify candidate microbial taxa, metabolites, and host gene signatures associated with disease outcomes. RCTs are required to establish causality and evaluate efficacy of microbiome-targeted interventions (e.g., probiotics, prebiotics, defined microbial consortia, metabolite supplementation, or FMT derivatives).

## 2. Preclinical and Regulatory Requirements

• Compile preclinical safety and mechanism data (in vitro, ex vivo, and animal models).

• Engage Institutional TTO for IP considerations and DCGI/CTRI for regulatory pathway. For live biotherapeutics or FMT derivatives, follow DCGI guidance and obtain necessary approvals.

• GMP manufacturing requirement for microbial products; outline contract manufacturing organization (CMO) options.

## 3. Pilot Study Design

• Objectives: Safety, feasibility, and biological signal (changes in microbiome and host transcriptomics).

• Design: Randomized, placebo-controlled or open-label depending on intervention; small sample size (n=30–100) to assess safety and biological endpoints.

• Endpoints: Safety/tolerability, microbiome shifts, changes in host gene-expression biomarkers, and preliminary clinical signals (e.g., HbA1c change in T2DM; sputum conversion in TB).

## 4. Definitive RCT Design Considerations

• Sample size: powered on primary clinical endpoints informed by pilot effect sizes. For T2DM, primary endpoint could be change in HbA1c at 6 months. For TB, primary endpoint could be treatment success/relapse rate at 12 months post-treatment.

• Randomization, blinding, stratification (by baseline microbiome signature), and allocation concealment details to be specified in full protocol.

• Data Safety Monitoring Board (DSMB) to oversee safety; interim analyses planned for efficacy/safety stopping rules.

## 5. Operational & Logistical Considerations

• Site selection based on ecological hotspots and cohort findings; ensure laboratory and cold-chain capacity.

• Training materials, SOPs, and monitoring plans for sites; central lab for sequencing and standardized bioinformatics pipelines.

• Data management plan, eCRFs, and trial registration in CTRI prior to enrollment.

## 6. Ethical & Community Considerations

• Community engagement and informed consent processes, especially for interventions involving live organisms or donor-derived materials (FMT).

• Plans for adverse event reporting, management, and compensation per Indian regulations.

## 7. Timeline & Milestones

• Months 0–6: Preclinical work and pilot study protocol development; regulatory engagement and GMP sourcing.

• Months 6–18: Pilot trial execution and analysis.

• Months 18–36: Definitive RCT planning and execution pending pilot results and funding.