IMPAACT 2020: **S**hortened Oral Treatment for **M**ultidrug-**R**esistant **T**uberculosis in Children (SMaRT Kids): A Phase III Randomized Multi-center Trial

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Background and Rationale (1)

- *1. Public health relevance:* Substantial global burden of MDR-TB in children
- *2. Improved treatment is needed:*
  - Current regimens long (9-18m), toxic (20% hearing loss) and poorly tolerated
  - Different implications for children – hearing loss, hospitalization - during critical periods of neurodevelopment, attachment
  - New WHO-recommended 9-11m regimen still contains injectable x 4m

Background and Rationale (3)

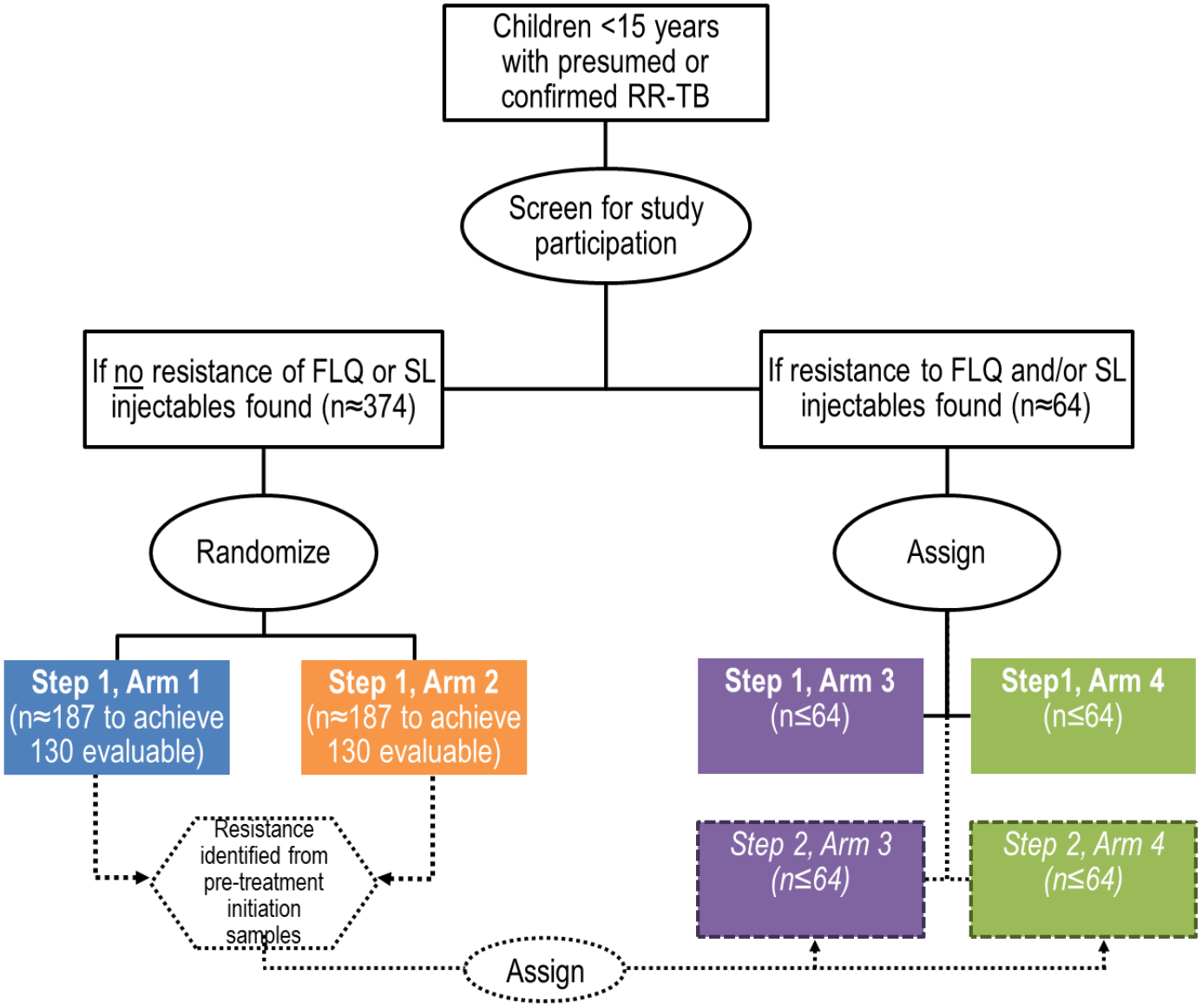
- *3. Need for efficacy trial in children*
  - Children tend to have paucibacillary TB (less severe)
    - Reasonably expected to respond better to treatment than adults
  - MDR-TB treatment outcomes
    - Adults – 50% successful outcome
    - Pediatric – 75-90% successful outcome

Background and Rationale (4)

- *Summary:*
  - Children may suffer disproportionately from existing treatment regimens…
  - …AND would be expected to respond better than adults to shorter, less intense regimens
  - Time is right –
    - More children being diagnosed
    - New and repurposed treatments becoming available

Design (1)

- Design: Phase III, partially-randomized, open-label multi-center trial
- Inclusion
  - Children 0 to <15 years of age;
  - Probable or confirmed pulmonary or extrapulmonary RR-TB +/- additional SLI or FQN-Res (i.e. pre-XDR and XDR-TB)
  - HIV-infected and uninfected
- Exclusion
  - Probable or confirmed Stage 2 or 3 TB meningitis or osteoarticular TB.


Children <15 years with presumed or confirmed RR-TB
Screen for study participation
If no resistance of FLQ or SL injectables found (n≈374)
If resistance to FLQ and/or SL injectables found (n≈64)
Randomize
Assign
Step 1, Arm 1 (n≈187 to achieve 130 evaluable)
Step 1, Arm 2 (n≈187 to achieve 130 evaluable)
Step 1, Arm 3 (n≤64)
Step1, Arm 4 (n≤64)
Resistance identified from pre-treatment initiation samples
Step 2, Arm 3 (n≤64)
Step 2, Arm 4 (n≤64)
Assign

Intervention

- Children with MDR/RMR randomized 1:1 to control vs intervention arms
- Children with preXDR/XDR assigned to treatment arm based on resistance profile

Proposed treatment regimens by drug-resistance profile and study arm	
MDR/RMR TB	
Arm 1 Intervention	8 wks DLM, BDQ, LZD, LFX / 18 wks DLM, BDQ, LFX
Arm 2 Control	16 wks AMK, LFX, ETO, CFZ, PZA, hdINH, EMB / 24 wks LFX, CFZ, PZA, EMB
preXDR/XDR-TB	
Arm 3 FQN-susc	8 wks DLM, BDQ, LZD, LFX / 18 wks DLM, BDQ, LFX
Arm 4 FQN-res	8 wks DLM, BDQ, CFZ, LZD / 18 wks DLM, BDQ, CFZ

Objectives

- *Primary Objectives*
  - Determine whether an all-oral, short-course regimen (Arm 1) is non-inferior to the WHO-recommended, shortened injectable-containing regimen (Arm 2) with regard to a favorable outcome through Week 72
  - Compare the safety and tolerability between an all-oral, short-course regimen (Arm 1) and the WHO-recommended, shortened injectable-containing regimen (Arm 2) through Week 48
- *Secondary Objectives*
  - Characterize the cardiac safety of co-treatment with BDQ and DLM through Week 26
  - Outcomes/safety for RRi-TB and RRf-TB, PK, acceptability, cost-effectiveness
- *Exploratory Objectives*
  - Others – biomarkers, novel trial design [desirability of outcome rankings (DOOR)]

Sample Size

- Efficacy: 374 (187 per arm) to demonstrate non-inferior efficacy of intervention arm among children with probable or confirmed RR-TB with 90% power
  - Assumptions:
    - 12% non-inferiority margin
    - 85% (ctrl) and 87% (int) successful outcomes
    - 30% non-evaluable
  - 130 evaluable
- Safety: 80% power to detect superior safety of intervention arm

Study duration and progress

- Study duration
  - 30 months to complete enrolment - 12 participants/month
  - 54 months to complete follow-up
- Protocol development ongoing
  - First full draft near completion
  - V1 Q4 2018/Q1 2019
- Sites
  - 10 indicated interest
  - Drafting SIP

Potential impact

- Impact international guidance for MDR-TB treatment in children
- The proposed trial will also:
  - Microbiological and clinical/radiological treatment response in children with TB
  - Experience with novel/repurposed TB drugs which are the future of TB treatment, even if in different regimens
  - Build international capacity for pediatric TB trials
  - Catalyze diagnosis and treatment of children with MDR-TB
- Acknowledments: 2020 Protocol Team