IMPAACT 2020: **Shortened Oral Treatment for Multidrug-Resistant Tuberculosis 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
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)

Randomize

- **Step 1, Arm 1** (n≈187 to achieve 130 evaluable)
  - Resistance identified from pre-treatment initiation samples

- **Step 1, Arm 2** (n≈187 to achieve 130 evaluable)

If resistance to FLQ and/or SL injectables found (n≈64)

Assign

- **Step 1, Arm 3** (n≤64)

- **Step 1, Arm 4** (n≤64)

Assign

- **Step 2, Arm 3** (n≤64)

- **Step 2, Arm 4** (n≤64)
**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

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

- Acknowledgments: 2020 Protocol Team