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SP30 Novel strategies to accelerate tuberculosis treatment in children:

Statistical trial design considerations and innovative approaches to pediatric Phase III trials

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✓ I have no, real or perceived, direct or indirect conflicts of interest that relate to this presentation.

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FDA Extrapolation Framework for Pediatric Labeling

- Because of their differing spectrum of TB disease compared to adults (more likely to be non-severe, paucibacillary, smear- and culture-negative), children may have better outcomes when treated with TB regimens that contain fewer drugs, are of shorter duration, and in the context of MDR-TB, are injectable-sparing.
- Extrapolation from adults may result in the dismissal of regimens that may benefit children.
For children, the benefits of novel treatment regimens may go beyond efficacy and short term safety.
- Palatable/tolerable regimens may be more important.
- For MDR-TB treatment, injectable-sparing regimens are expected to reduce permanent hearing loss resulting in better neurodevelopmental and other long term outcomes (e.g. educational) in children often not measured in an RCT.

These differences have implications for study design and feasibility.
Study Design Considerations for TB Treatment Trials in Children

- Entry points; who to study
- Outcome definitions
- For treatment shortening trials
  - when to assess the outcome
  - durations to study
Challenges of TB Treatment Trials: Entry Points

- Microbiological confirmation and DST are available in only 30-40% of children.
- Even when results are ultimately available, they may be delayed until after study entry.
Challenges of TB Treatment Trials: Entry Points

Why not include only confirmed TB cases and exclude those with clinically diagnosed TB?
• Children with clinically diagnosed TB may be more likely to have minimal, paucibacillary disease, and might represent the subgroup most likely to benefit from the test treatment regimen (e.g., shorter, all-oral treatment).
• Children with clinically diagnosed TB are a large portion of the population of children with TB and urgently need evidence-based efficacious treatment.

Why not wait until final TB diagnostic results are available?
• It may not be in best interest of the child to delay randomization and initiation of Rx.
Solutions: Entry Points

• Enroll both confirmed and clinically-diagnosed TB cases.
• Use the adult contact’s TB diagnostic and DST results, coupled with well-defined signs/symptoms and radiology, to clinically-diagnose TB.
• No data from post-randomization samples should be used in defining analysis populations.
• Exclusions of participants based on final (possibly delayed) DST are ok, but are based on samples collected prior to randomization applied equally to all arms.
• Subgroup analysis performed by confirmation status can be done.
Implications of Entry Points on Study Outcomes

• Clinically-diagnosis of TB creates downstream challenges for defining outcomes, because it precludes the use of culture conversion in the outcome definition.

Solutions

• Use well-defined definitions of probable cure and clinical relapse based on clinical (including radiological) evidence (see SHINE study*, IMPAACT 2020/SMaRT Kids).
• Review by Independent Outcomes Committee.

Composite Primary Efficacy Outcomes

Should focus on measures of treatment efficacy and be well defined for confirmed and clinically diagnosed TB cases:

1. Treatment failure, including clinical failure
2. Recurrence, probable recurrence (for clinically diagnosed TB)
3. Death
4. Others?: Drug changes, discontinuations, extensions; LFU

The components will affect sample size, and in non-inferiority trials, the NI margin.
Timing of Outcome Assessment When Treatment Durations Differ

Options 1: Rx failure at EOT, common relapse duration

Options 2: Rx failure at EOT, relapse period ends at common time post-randomization

Options 3: Common Rx failure and relapse periods (may fail prior to EOT on short regimen)
Considerations for Timing of Outcome Assessment When Treatment Durations Differ

- Post-treatment follow-up duration should be sufficiently long to capture the majority of relapses for both arms. 75% of recurrence occur within 6 months, and 90% within one year post-Rx.*
- Option 1: while intuitive, may not be the best primary evaluation period for a clinical trial because overall follow-up differs; bias favors shorter test Rx. It may be useful to report for compliance with clinical practice/guidelines.
- Options 2&3: Same overall follow-up, but post-treatment follow-up is longer on the shorter regimen → more opportunity for relapse; bias favors the longer control Rx.

**Treatment Shortening Studies with Multiple Shortened Durations**

Example: Standard duration control vs 3 and 4-month test regimens with pairwise comparisons of shorter test treatments to standard duration for non-inferiority. Multiple comparisons require control of type I error (falsely declaring non-inferiority of a regimen).

- Bonferroni approach (split type I error by number of comparisons)
- Hierarchical testing: Useful when the same drugs are used in the test regimens.
  - Test 4-month regimen first, if it is efficacious, then test 3-month regimen.
  - May not test the shortest regimen at all.
Avoids the situation when selected duration(s) is too short or can be further shortened.

Randomize participants to control or several durations of new regimen.

Model the duration response curve.

Identify minimum non-inferior duration using confidence intervals.

Duration-Response Design*

Duration-Response Model

- More informative than testing 1-2 durations.
- Potential to be more powerful than traditional two-sample comparison by borrowing information from several different durations.
- Can interpolate and estimate minimum duration needed to achieve an acceptable (non-inferior, or possibly superior) durable cure rate.
- Properties of estimator not yet fully developed for use in regulatory setting.

Adapted from Ritesh Ramchandani, ACTG TB Think Tank 2018
Risk-Benefit Approach

• Assesses regimens based on the totality of a participant’s experience based on factors such as efficacy, AEs, QoL, etc using a single unified outcome that accounts for the differing importance of the heterogeneous events.

• First proposed by Chuang-Stein (Statistics in Medicine, 1991), Follmann et al. constructed ranking scheme for cardiovascular disease trials (Statistics in Medicine, 1992), Evans et al. generalized and called it a Desirability of Outcomes Ranking (DOOR) outcome in the context of antibiotics stewardship trials (Clinical Infectious Diseases, 2015)

• Montepiedra et al. proposed a using a DOOR outcome in the context of TB.

Benefits of Risk-Benefit Approach

- For a regimen with slightly lower efficacy that has other benefits that make it attractive, we can evaluate its superiority using the composite DOOR outcome that reflects a participant’s overall clinical experience.

Hypothetical Example

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable Efficacy</td>
<td>83%</td>
<td>✓ 85%</td>
</tr>
<tr>
<td>Treatment limiting AEs</td>
<td>✓ 5%</td>
<td>20%</td>
</tr>
</tbody>
</table>
### Example Ranking Assuming Efficacy Has Priority over Safety

<table>
<thead>
<tr>
<th>Ranking (4 = Best, 1 = Worst)</th>
<th>Composite Outcome</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unfavorable &amp; Rx-limiting AE</td>
<td>Unfavorable &amp; Rx-limiting AE</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable &amp; No Rx-limiting AE</td>
<td>Unfavorable &amp; No Rx-limiting AE</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Favorable &amp; Rx-limiting AE</td>
<td>Favorable &amp; Rx-limiting AE</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Favorable &amp; No Rx-limiting AE</td>
<td>Favorable &amp; No Rx-limiting AE</td>
<td></td>
</tr>
</tbody>
</table>
Example Ranking Assuming Efficacy Has Priority over Safety

<table>
<thead>
<tr>
<th>Ranking (4 = Best, 1 = Worst)</th>
<th>Composite Outcome</th>
<th>Test Arm</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy &amp; Safety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Unfavorable &amp; Rx-limiting AE</td>
<td>0.85%</td>
<td>3%</td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable &amp; No Rx-limiting AE</td>
<td>16.15%</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>Favorable &amp; Rx-limiting AE</td>
<td>4.15%</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>Favorable &amp; No Rx-limiting AE</td>
<td>78.85%</td>
<td>68%</td>
</tr>
</tbody>
</table>

\[ P(T>C)=26.4\% \text{ } \& \text{ } P(C>T)=17.4\%: \text{ } \text{hence the test treatment better.} \]

In a trial, use a rank based method for statistical comparison.
Developing the Rankings

• The rankings are inherently subjective.
• Consensus process to inform the development of rule-based ranking scheme or a Delphi process.
• The panel of stakeholders can include clinicians, public health authorities, and patients/caregivers.
• For a clinical trial the rankings should be developed prior to enrolling participants.

Risk-Benefit Approach Summary

- It can incorporate other aspects of a participant’s experience, including patient reported outcomes.
- Weights can also be used to give more importance to certain outcomes in the composite.
- Attractive approach because it reframes the question as one of superiority.
- Requires experience with this approach using data from TB treatment studies.
- It is being used in secondary analysis of ACTG (A5279*) and IMPAACT (P1060 DACS 701, P1078) studies.
- Properties of the estimators are in development.

Conclusion

- Given the spectrum of TB disease in children, there is potential for efficacious, safe, tolerable, or shorter regimens that extrapolation from adults would not identify.
- When extrapolation is inappropriate, efficacy studies should be conducted in children and can be done maintaining high standards.
- International and national guidance on TB treatment in children are outpacing our ability to perform the research needed to underpin strong recommendations based on highly quality data. As a research community we need to rapidly design and conduct high quality studies ahead of recommendations.
Acknowledgments

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