Trial Design Considerations in Developing Pediatric Master Protocols

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Background

• Up to 40% of pediatric trials fail to establish safety or efficacy and result in a labeled indication for pediatric use

• Trial Design Challenges
  – Inappropriate endpoints
  – Placebo effects
  – Feasible designs for small populations
Objectives

• Review efficacy/response endpoints measured in pediatric clinical trials since 2007, and highlight issues that should be resolved prior to a master protocol

• Discuss placebo considerations in pediatric trials

• Hypothesize trial designs that may be amenable to the use of a master protocol in the pediatric population
Endpoints in Pediatric Efficacy Trials

• Efficacy endpoints that are well-defined, reliable, and interpretable are critical to trial success

• The use of inappropriate or unvalidated endpoints in pediatric trials has led to trial failure

• Endpoints used in adult trials may not always be suitable for pediatrics

• Characteristics of the endpoint may influence trial outcome

<table>
<thead>
<tr>
<th></th>
<th>FDAAA</th>
<th>FDASIA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Trials</td>
<td>133</td>
<td>103</td>
<td>236</td>
</tr>
<tr>
<td>Total Unique Drugs</td>
<td>83</td>
<td>68</td>
<td>138</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial Outcome</th>
<th>FDAAA (%)</th>
<th>FDASIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>75.9</td>
<td>77.7</td>
<td>76.7</td>
</tr>
<tr>
<td>Failure</td>
<td>24.1</td>
<td>22.3</td>
<td>23.3</td>
</tr>
</tbody>
</table>

*Inconclusive trials were considered to have failed

<table>
<thead>
<tr>
<th>Label Outcome</th>
<th>FDAAA (%)</th>
<th>FDASIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>83.5</td>
<td>74.8</td>
<td>79.7</td>
</tr>
<tr>
<td>Not approved</td>
<td>16.5</td>
<td>25.2</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*Drugs approved in a subset of the full age range studied were considered to have been approved

**Represents preliminary data
Label Outcome by Therapeutic Area**

**Represents preliminary data
## Endpoint Characteristics**

<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>FDAAA (%)</th>
<th>FDASIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective</td>
<td>43.6</td>
<td>41.7</td>
<td>42.8</td>
</tr>
<tr>
<td>Objective</td>
<td>46.6</td>
<td>52.4</td>
<td>49.2</td>
</tr>
<tr>
<td>Both</td>
<td>9.8</td>
<td>5.8</td>
<td>8.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>FDAAA (%)</th>
<th>FDASIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Outcome</td>
<td>46.6</td>
<td>36.9</td>
<td>42.4</td>
</tr>
<tr>
<td>Surrogate</td>
<td>42.9</td>
<td>54.4</td>
<td>47.9</td>
</tr>
<tr>
<td>Both</td>
<td>10.5</td>
<td>8.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

**Represents preliminary data
Study Endpoint Type by Therapeutic Area**

**Represents preliminary data
Trial Outcome by Endpoint Type**

**Represents preliminary data
Combined Adult & Pediatric Trials**

• 44 drugs were studied in combined adult & pediatric trials
• Most frequent therapeutic areas:
  – Allergy (e.g. allergic rhinitis)
  – Dermatology (e.g. acne)
  – Pulmonary (e.g. asthma)
  – Oncology (e.g. ALL)
• When the disease in pediatric patients and adults is the same, this is a reasonable approach for master protocols

*Trials that enrolled patients less than and greater than 18 years of age were considered combined trials

**Represents preliminary data
Trial Outcome for Combined vs. Separate Studies**

**Represents preliminary data
Comparison of Adult and Pediatric Endpoints**

<table>
<thead>
<tr>
<th>Adult Endpoint</th>
<th>FDAAA (%)</th>
<th>FDASIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as Pediatric</td>
<td>63.2</td>
<td>57.3</td>
<td>60.6</td>
</tr>
<tr>
<td>Different than Pediatric</td>
<td>36.8</td>
<td>42.7</td>
<td>39.4</td>
</tr>
</tbody>
</table>

*Endpoints were considered different when the outcome measure was different and/or when the time point of measurement was different

**Represents preliminary data
**Trial Outcome by Same Endpoint Used**

**Represents preliminary data**

**Percentage of Studies (%)**

- **Same**
  - Success: 124 (50% FDAAA, 50% FDASI)
  - Failure: 19 (20% FDAAA, 80% FDASI)

- **Different**
  - Success: 57 (30% FDAAA, 70% FDASI)
  - Failure: 36 (20% FDAAA, 80% FDASI)
Consistency in Endpoint Selection**

• Total of 66 indications studied across 236 trials

• For 42% (28/66) of the indications, at least 2 or more drugs were studied [median 2.5; range 2-16]

• For 80% (22/28) of the indications, the endpoint and/or time of measurement differed across the various drug trials for that indication

• Consensus by the sponsors and regulatory agencies on the optimal efficacy endpoint for a given indication is an important step prior to developing a disease-specific master protocol

**Represents preliminary data
Placebo Use in Pediatric Trials

• There are ethical constraints for the use of placebos in pediatric research

• High placebo responder rates in children have been problematic in previous drug development trials (e.g. MDD, migraine)

• Placebo response in pediatric patients in US may differ from other parts of the world (e.g. Europe)

Source: CDER Rounds. Review of Migraine Therapeutics in Adolescents: An Example of Failed Pediatric Trials. HaihaoSun MD, PhD
Placebo Use in Pediatric Trials (cont.)

- Large placebo effects limit the ability to detect effective therapies
- Understanding factors contributing to placebo response is critical
- Strategies for reducing placebo response rates should be considered

Two-Stage Double-Randomization Design

Trials Designs Appropriate for Small Patient Populations

• Many trial designs may be amenable to master protocols
• Selection of designs that are feasible and efficient in pediatrics is key (due to small populations, recruitment challenges, etc.)
• Examples of randomized, comparative trial designs with potential for master protocols:
  – Parallel
  – Cross-over
  – Randomized withdrawal
  – Adaptive
Summary - 1

• Master protocols have potential for use in pediatric product development – but the details are very specific to the disease process;

  – Certain therapeutic areas remain problematic for pediatric trial success; so master protocols in these areas may be difficult at this time

  – When endpoints measured in adults vs. pediatrics were different, fewer trials were successful

  – Understanding the disease process and selecting appropriate endpoints are a critical part of planning for master protocols
Summary - 2

– Including pediatric patients and adults in a single master protocols may be a reasonable approach when possible

– Strategies for managing the use of placebo in pediatric clinical trials may require further discussion

– Multiple trial designs for small patient populations have the potential to be amenable to the development of master protocols