Multiplicity Issues in Biologics Clinical Trials: Regulatory Perspectives

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Outlines

FDA/CBER/Division of Biostatistics

Multiplicity Issues/Guidance in Clinical Trials

Multiplicity Issues in Vaccine Trials:

- Combination vaccines
- Vaccines with multiple serotypes
- Therapeutic vaccines
- Concomitant vaccines
- Composite endpoints in vaccine trials
Food and Drug Administration (FDA)

- Center for Biologics Evaluation and Research (CBER)
  - Office of Vaccines Research and Review
  - Office of Blood Research and Review
  - Office of Cellular, Tissue, and Gene Therapy
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- National Center for Toxicological Research (NCTR)
CBER Division of Biostatistics

- Vaccine Evaluation Branch supports the Office of Vaccines Research and Review
  - Viral and Bioassay Team
  - Bacterial and Allergenic Team

- Therapeutics Evaluation Branch supports the Office of Cellular, Tissue and Gene Therapies and the Office of Blood Research and Review
  - Blood Therapeutics and Devices Team
  - Diagnostics and Screening Tests Team
  - OCTGT Therapeutics and Devices Team
Statistical Review
Vaccine Products/Disease Areas

- Bioterrorism/Pandemic (Smallpox, Anthrax, Plague, Influenza, Botulism)
- Prophylactic Vaccines: (Hepatitis, Meningococcal, Pneumococcal, HIV, Human Papillomavirus, Measles / Mumps / Rubella / Varicella, Diphtheria / Tetanus / Pertussis, Poliovirus)
- Cancer Vaccines (Prostate, Lymphomas, Melanomas)
Statistical Review
Other Products/Disease Areas

- Tissue/Cell Therapy (Islets transplantation in Type I Diabetes)
- In Vitro Diagnostic Test Kits for blood safety (HIV, Hepatitis, West Nile Virus, Human T-Lymphotropic Virus)
- Devices used in processing blood products or in delivery of a biologic at point of care
Multiplicity Issues

- Multiple Endpoints in studies
- Composite endpoints
- Primary and secondary endpoint(s)
- Multiple Trials
- Subgroup Analyses
General Guidance

- Type I error rate for each elementary hypothesis must be controlled at $\leq \alpha$ (.05, .01, .001, ...)

- Family of comparisons: Doses and endpoints under testing are all considered in the family (including all intersection hypotheses)

- Control study-level (family-wise) type I error rate (i.e., max type I error rate) at $\leq \alpha$ (.05, .01, .001)

- “Strong control”
Strong control

- Strong control at the study level treats all studies ‘equally’ in regulatory applications.
- For each trial, the more hypotheses are tested, the more statistical adjustments and more planning on statistical decision tree needed.
- A principle generally followed by the statistical community is to control “experiment-wise” type I error rate, as the clinical trial is an experiment.
- Doesn’t control multiplicity on multiple trials.
Multiplicity and Type I & Type II Errors

- Multiplicity poses a critical challenge to product licensing
- We simultaneously recognize the genuine scientific need for multiple endpoints in a variety of contexts, and are also very concerned that all clinical trials maintain adequate control of Type 1 error.
- Maintaining strong control of Type I error in the presence of multiplicity can mean inflation of Type II error: false negatives.
Multiplicity Issues in Vaccine Trials:

- Combination vaccines
- Vaccines with multiple serotypes
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- Composite endpoints in vaccine trials
Combination Vaccines

- Examples: DTaP, MMRV, DTaP/IPV, DTaP/HBV/IPV, MMRV vs. MMR + Varicella
- Need to be non-inferior for each of the diseases (components) when compared to separate administrations
- Potential interactions/interference between the vaccine components
- Safety
Vaccines with Multiple Serotypes

- Comparison between licensed n-valent vs. new (n+k)-valent

- Examples:
  - Pneumococcal 7-valent vs. 13-valent
  - Influenza trivalent vs. quadrivalent
  - H1N1/H3N2/B vs.
    - H1N1/H3N2/B1/B2
    - H1N1/H3N2/B1
    - H1N1/H3N2/B2
Vaccines with Multiple Serotypes (2)

- When compared to licensed vaccine, non-inferiority test for core serotypes is considered. Then, what would be the endpoint(s) for additional serotypes?
- When adding new serotype(s), how to evaluate risk/benefit?
- Sample size/Power issues
Therapeutic Vaccines

- Examples:
  - HIV
  - Herpes virus
  - Tumor vaccines

- Multiple relevant efficacy endpoints:
  - Overall survival
  - Progression-free survival
  - Morbidity
  - Response rate, duration
  - CD4 counts, viral load, … → definite endpoint

- Withdrawal is an important factor for the choice of endpoints.
Concomitant vaccines

- **Examples:**
  - DTaP+Hib+IPV+PCV7
  - Hib+PCV7+MMR

- **Evaluate safety in particular and immunogenicity in the presence of concomitant vaccines**

- **Interaction(s):** When multiple vaccines are concomitantly administered, some vaccinees may exhibit reduced immune response or increased reactogenicity
Multiple vs. Composite Endpoints

- Test two or more separate endpoints:
  - Combine the results via Fisher’s method or multiplicity adjustment

- Create a single composite measure
  - Capture vaccine effect in more than one dimensions
  - Validation issues

<table>
<thead>
<tr>
<th></th>
<th>CD4 +</th>
<th>CD4 -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load +</td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Viral Load -</td>
<td>(3)</td>
<td>(4)</td>
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</table>
Vaccines for diseases with composite endpoints

- For some diseases (such as zoster and HIV), vaccines are targeted to reduce the incidence and/or the severity of the disease (prolong development, delay full blown)
- Combine preventive and therapeutic aspects of a vaccine
- Define a clinically meaningful change in severity endpoints
Subgroup Analyses
Post-hoc subgroup results may show an increase/decrease in efficacy/safety different from overall results

MI-CP111 Safety Results on Safety population
Relative Risk of FluMist to TIV
Based on All-Cause Hospitalization

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>CAIV-T N</th>
<th># of Subjects with All-Cause Hospitalization</th>
<th>TIV N</th>
<th># of Subjects with All-Cause Hospitalization</th>
<th>Relative Risk of FluMist Compared to TIV (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>6 ~ 59</td>
<td>4179</td>
<td>45 (1.1%)</td>
<td>4173</td>
<td>45(1.1%)</td>
<td>1.00 (0.66, 1.50)</td>
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<tr>
<td>6 ~ 23</td>
<td>1992</td>
<td>32 (1.6%)</td>
<td>1975</td>
<td>24 (1.2%)</td>
<td>1.32 (0.79, 2.22)</td>
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<tr>
<td>6 ~ 11</td>
<td>684</td>
<td>15(2.2%)</td>
<td>683</td>
<td>9 (1.3%)</td>
<td>1.66 (0.75, 3.70)</td>
</tr>
<tr>
<td>12 ~ 23</td>
<td>1308</td>
<td>17 (1.3%)</td>
<td>1292</td>
<td>15 (1.2%)</td>
<td>1.12 (0.57, 2.20)</td>
</tr>
</tbody>
</table>
That is it.

Thanks for the time and listening!