Interim Analysis Strategies for Adaptation In Seamless Phase II/III Vaccine Trials

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Agenda

- Introduction
  - “Keep-the-Winner” Design (New HPV Vaccine)
- Group Sequential Design (S. aureus Vaccine)
- Group Sequential Vaccine Efficacy Studies
Introduction: Definitions

- **Seamless Phase II/III design:** refers to a design that combines a traditional Phase IIb study and traditional Phase III study into a single study.
  - Traditional studies analyzed separately and independently

- **Adaptive design:** refers to a design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the *validity* and *integrity* of the trial

- **Adaptive Seamless Phase II/III design:** refers to a seamless design that uses data from before and after the adaptation in the final analysis
Adaptive Designs

- New paradigm of clinical development: **Learn and Confirm**

- Build adaptive features in clinical trials to provide a “window” of opportunity to adjust the trial based on interim data
  - To accelerate the clinical development by reducing the time gaps (“white” spaces) between studies

- Adapt by design and not *post hoc* as a remedy
Adaptive Design Features

- Change of doses (dose-response curve)
- Change of populations (enrichment)
- Drop the “losers”
- Adjust sample size
- Seamless phase II/III trial
Introduction: Adaptation Benefits

- More efficient, faster trials
  - Process efficiency for Clinical Trials
  - Midcourse correction for trials that are off target
  - Fewer patients enrolled into ineffective treatment arms
    - Shorter trials – smaller overall sample size required
    - Increased quality of results – more patients enrolled into successful treatments
    - Better for patient volunteers – greater chance of receiving an effective treatment

- Reduce timeline by combining phases
  - Reduce white space between phases
  - Reduce overall time of Clinical Development

- Reduce costs by stopping unsuccessful trials early
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“Keep-the-Winner” Design
(New HPV Vaccine)

● **Study Design Goals**
  – Combine dose-ranging Phase IIb trial (Part A) with Phase III efficacy trial (Part B) to reduce development timelines.
  – Allow for early stopping if no dose is acceptable
  – Combine efficacy and immunogenicity data from both Part A and B for final analyses

● **Randomized, double-blind, GARDASIL™-controlled dose-ranging study**
  – 3-dose regimen of new HPV vaccine (3 formulations) or GARDASIL™ in healthy females 16-26 years of age

● **Efficacy outcomes** – prevention of cervical, vulvar, vaginal disease caused by the HPV types in the new HPV vaccine

● **Immunogenicity outcomes** – immunogenicity against HPV types contained in the new HPV vaccine.
“Keep-the-Winner” Design
(New HPV Vaccine)

Part A

Formulation 1

Formulation 2

Formulation 3

GARDASIL™

Part B

Formulation X
“Keep-the-Winner” Design: Challenges (New HPV Vaccine)

- **Selection of Dose in Part A**
  - Use of immunogenicity, but no accepted correlate of protection
  - Must be non-inferior to active control, but by what margin?

- **Logistics of Trial**
  - Efficient transition between Part A and Part B → IVRS
    - Turn off non-selected doses
    - Sufficient drug supply at sites for transition
  - Requires quick turnaround of assay testing
  - DMC for monitoring safety and making dosing decisions
  - Unblinded individuals needed for performing the interim analysis
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Group Sequential Design
(S. aureus Vaccine)

- **Study Design Goals**
  - Combine Proof-of Concept Phase IIb trial with Phase III efficacy trial to reduce development timelines.
  - Allow for early stopping for no efficacy or for super efficacy

- **Randomized, double-blind, group sequential, placebo-controlled study**
  - Single-dose of *S. aureus* vaccine (60 µg) vs. placebo in adults (>18 years of age) planning to undergo cardiothoracic (CT) surgery
  - Three interim analyses for futility and/or efficacy
  - Event-driven trial

- **Efficacy**
  - Primary: Proportion of patients with serious *S. aureus* infections at any time during the 90-day postoperative period
Group Sequential Design: Challenges
(S. aureus Vaccine)

- **Interim Analysis Strategy**
  - Timing of interim analyses; futility and efficacy boundaries at each analysis (more to come)

- **Logistics of Trial**
  - Internal resource planning:
    - Event-driven – when will interim analyses be reached?
    - When to declare POC? Requiring the same statistical criterion for a stand along Phase IIb POC trial not feasible.
  - Adjudication committee for adjudicating cases
  - DMC for monitoring safety and making decisions at interim analyses
  - Unblinded individuals needed for performing the interim analysis
Group Sequential Design: Challenges (S. aureus Vaccine)

- **Regulatory Interactions**
  - Acceptance of a combined Phase IIb and Phase III trial for new vaccine
  - Agreement on the statistical criterion needed for showing vaccine efficacy
  - Acceptance on potential for stopping early for success
    - Stopping early? Make sure you are clearly above the statistical criterion
    - Boundaries at interim analyses chosen to meet statistical criterion, but would safety database be sufficient in size?
    - Even if statistical criterion is met early, still need to collect sufficient safety follow-up.
  - Even more critical to maintain internal blinding
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Group Sequential Vaccine Efficacy Studies

Efficacy Hypothesis of Interest:

\[ H_0: V_E \leq \delta \]

\[ H_1: V_E > \delta \quad \text{where,} \]

- \( V_E = 1 - RR \) is the vaccine efficacy
- \( RR \) is the relative risk of the vaccine compared to placebo
- \( \delta \) is the prescribed success criterion (e.g., \( \delta = .25 \) for Gardasil™)
Let $S_v$ and $S_p$ be the number of cases in the vaccine and placebo groups, respectively.

Assume $S_v$ and $S_p$ are independent Poisson random variables with means $\lambda_v$ and $\lambda_p$.

Then given $S_v + S_p$, $S_v$ is binomially distributed with parameters $S_v + S_p$, and $p = \lambda_v / (\lambda_v + \lambda_p)$

- $p$ is the probability that, among the cases, a subject in the vaccine group is a case
Group Sequential Vaccine Efficacy Studies: 
Exact Conditional Testing Approach

Following Chan and Bohidar (1998),

\[ H_0: V_E \leq \delta \text{ versus } H_1: V_E > \delta \]

is equivalent to

\[ H_0: p \geq p_0 \text{ versus } H_1: p < p_0 \]

\[ p_0 = \frac{(1-\delta)}{(2-\delta)}, \text{ when } N_p \approx N_v \text{ (i.e., 1:1 randomization)} \]

Using this testing approach, the sample size for the study is driven by the number of events needed to be observed.
Group Sequential Vaccine Efficacy Studies: 
Exact Conditional Testing Approach

Total # of Subjects (Cases) Required to Conclude Vaccine Efficacy > δ 
(~90% power, 2% Placebo Infection Rate, one-sided α = 0.025)

<table>
<thead>
<tr>
<th>δ</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6668 (95)</td>
<td>4364 (58)</td>
<td>2998 (37)</td>
<td>2106 (24)</td>
</tr>
<tr>
<td>0.10</td>
<td>9336 (133)</td>
<td>5640 (75)</td>
<td>3646 (45)</td>
<td>2458 (28)</td>
</tr>
<tr>
<td>0.20</td>
<td>14810 (211)</td>
<td>7746 (103)</td>
<td>4618 (57)</td>
<td>2984 (34)</td>
</tr>
<tr>
<td>0.25</td>
<td>19932 (284)</td>
<td>9550 (127)</td>
<td>5346 (66)</td>
<td>3336 (38)</td>
</tr>
</tbody>
</table>

δ = success criterion
VE = Vaccine Efficacy

Given the size of the trial, it is desirable to have interim analyses to check for futility or early success.
Group Sequential Vaccine Efficacy Studies:
Group Sequential Tests

A group sequential $K$-stage one-sided test of $H_0: p \geq p_0$ versus $H_1: p < p_0$ can be expressed in terms of the cumulative number of vaccine cases at stage $k$ ($S_k$) and has the general form (Jennison and Turnbull, 2000):

After group $k = 1, \ldots, K-1$

- if $S_k \geq b_k$ stop, accept $H_0$
- if $S_k \leq a_k$ stop, reject $H_0$
- otherwise continue to stage $k+1$,

After group $K$

- if $S_K \geq b_K$ stop, accept $H_0$
- if $S_K \leq a_K$ stop, reject $H_0$,

where $a_k$ and $b_k$, $k=1,\ldots,K$, are the success and futility boundaries, respectively, at the $k^{th}$ stage.
Jennison and Turnbull (2000) provide recursive formulas for calculating (exact) power, Type I errors, p-values, and confidence intervals at a given stage which account for the previous stages.

The Clinical Team must decide on the timing of the interim analyses (based on the number of cases observed) and the futility/success boundaries.

The Statistician must monitor the impact of these decisions on the power and Type I error for the study.

The discreteness of the Binomial distribution can make things interesting.
Group Sequential Vaccine Efficacy Studies: 
*Impact of Binomial Discreteness*

Total Number of Cases Required to Conclude Vaccine Efficacy > 0.25  
(\sim 90\% power, one-sided $\alpha = 0.025$)

<table>
<thead>
<tr>
<th>Total # Cases</th>
<th># Vaccine Cases</th>
<th>95% LB</th>
<th>$\alpha$ - level</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>19</td>
<td>0.281</td>
<td>0.0168</td>
<td>90.5</td>
</tr>
<tr>
<td>66</td>
<td>20</td>
<td>0.250</td>
<td>0.0249</td>
<td>93.5</td>
</tr>
<tr>
<td>67</td>
<td>20</td>
<td>0.268</td>
<td>0.0199</td>
<td>92.5</td>
</tr>
<tr>
<td>68</td>
<td>20</td>
<td>0.285</td>
<td>0.0158</td>
<td>91.4</td>
</tr>
<tr>
<td>69</td>
<td>21</td>
<td>0.255</td>
<td>0.0234</td>
<td>94.1</td>
</tr>
</tbody>
</table>

# Vaccine Case = maximum number of vaccine cases that would still conclude success  
95% LB = Lower bound of 95% CI if maximum number of vaccine cases is observed.
Group Sequential Vaccine Efficacy Studies:  
*Example Testing Strategy – 25% LB*

<table>
<thead>
<tr>
<th>Stages</th>
<th>Targeted Cases</th>
<th>Observed Vaccine Cases Futility/ Failure&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Observed Vaccine Cases for Success&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>Efficacy = 0%</th>
<th>Efficacy = 25%</th>
<th>Efficacy = 70%</th>
<th>Efficacy = 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cumulative Probability of Failure (%)</td>
<td>Cumulative Probability of Success (%)</td>
<td>Cumulative Probability of Failure (%)</td>
<td>Cumulative Probability of Success (%)</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>≥10</td>
<td></td>
<td>58.81</td>
<td>33.47</td>
<td>0.77</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>≥15</td>
<td>≤6</td>
<td>85.85</td>
<td>&lt;0.01</td>
<td>1.27</td>
<td>27.12</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>≥19</td>
<td>≤15</td>
<td>98.31</td>
<td>0.02</td>
<td>2.65</td>
<td>70.04</td>
</tr>
<tr>
<td>Final</td>
<td>69</td>
<td>≥22</td>
<td>≤21</td>
<td>99.91</td>
<td>0.09</td>
<td>6.51</td>
<td>93.49</td>
</tr>
</tbody>
</table>

<sup>†</sup> Futility corresponds to observed efficacy ≤0% in the vaccine group at Stage 1, observed efficacy ≤25% in the vaccine group at Stage 2, observed efficacy <43% in the vaccine group at Stage 3, and observed efficacy <54% in the vaccine group at the Final analysis.

<sup>‡</sup> Success corresponds to observed efficacy >79% in the vaccine group at Stage 2, observed efficacy >66% in the vaccine group at Stage 3, and observed efficacy >56% in the vaccine group at the Final analysis.
Group Sequential Vaccine Efficacy Studies: Additional Considerations

Ensure Overall Type I error is maintained even if futility analyses are ignored.

How do you handle situations where more than the planned number of cases are available at a given Stage?

An appropriate estimator for Vaccine Efficacy must be chosen.