

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

Part B

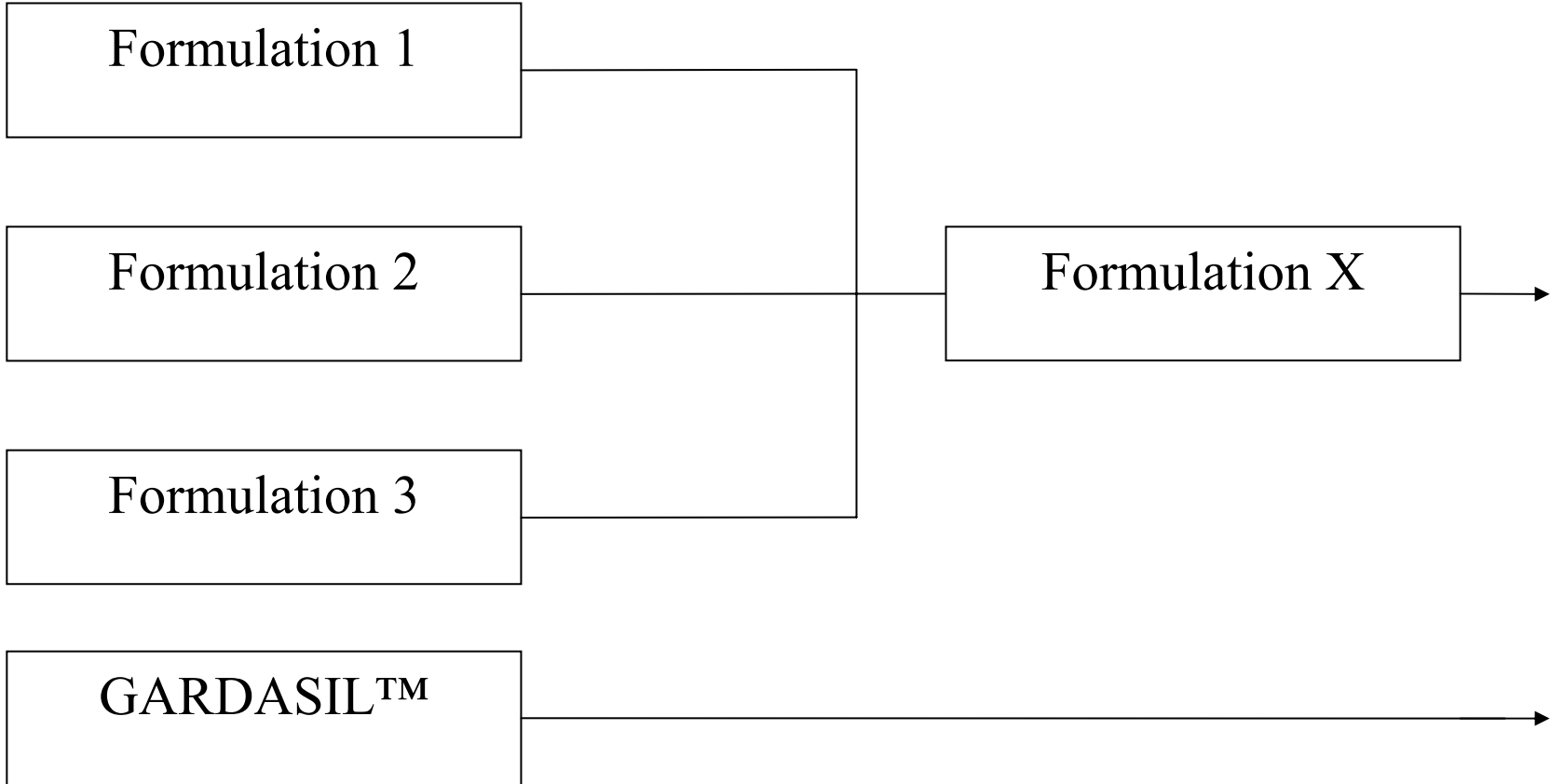
Formulation 1

Formulation 2

Formulation 3

GARDASIL™

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:

$$H_0: V_E \leq \delta$$

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

- $V_E = 1 - \text{RR}$ is the vaccine efficacy
- RR is the relative risk of the vaccine compared to placebo
- δ is the prescribed success criterion (e.g., $\delta = .25$ for GardasilTM)

Group Sequential Vaccine Efficacy Studies: *Exact Conditional Testing Approach*

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 λ_v and λ_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),

$H_0: V_E \leq \delta$ versus $H_1: V_E > \delta$ is equivalent to

$H_0: p \geq p_0$ versus $H_1: p < p_0$

– $p_0 = (1 - \delta) / (2 - \delta)$, when $N_p \approx N_v$ (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 $> \delta$
(~90% power, 2% Placebo Infection Rate, one-sided $\alpha = 0.025$)**

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

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 $k = 1, \dots, K-1$

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 , $k=1, \dots, K$, are the success and futility boundaries, respectively, at the k^{th} stage.

Group Sequential Vaccine Efficacy Studies: *Designing the Testing Plan*

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
(~90% power, one-sided $\alpha = 0.025$)**

Total # Cases	# Vaccine Cases	95% LB	α - level	Power (%)
65	19	0.281	0.0168	90.5
66	20	0.250	0.0249	93.5
67	20	0.268	0.0199	92.5
68	20	0.285	0.0158	91.4
69	21	0.255	0.0234	94.1

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

Stages	Targeted Cases	Observed Vaccine Cases Futility/Failure [†]	Observed Vaccine Cases for Success [‡]	Efficacy = 0%		Efficacy = 25%		Efficacy = 70%		Efficacy = 80%	
				Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)	Cumulative Probability of Failure (%)	Cumulative Probability of Success (%)
1	20	≥10		58.81		33.47		0.77		0.06	
2	35	≥15	≤6	85.85	<0.01	59.38	0.12	1.27	27.12	0.08	63.61
3	52	≥19	≤15	98.31	0.02	86.47	0.63	2.65	70.04	0.11	95.86
Final	69	≥22	≤21	99.91	0.09	97.62	2.38	6.51	93.49	0.21	99.79

[†] 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.

[‡] 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.