



Assessing Multiple Endpoints Using a Novel Software Solution in a Late-Stage Oncology Study

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Agenda

Background

Why multiple endpoints?

Generating Multiple Endpoint Data

Multi-State Models
Correlation-Based

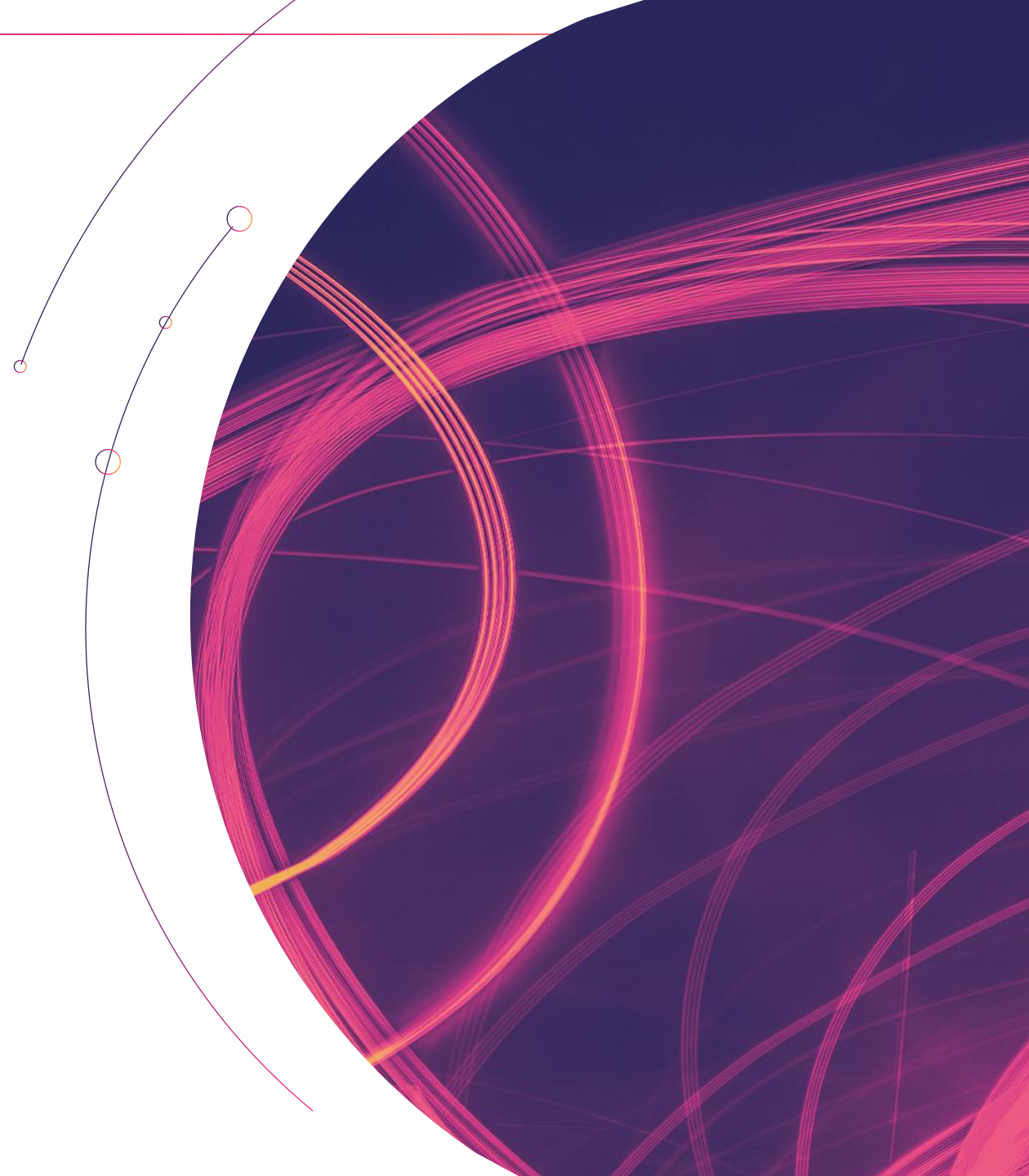
Multiplicity Control

Alpha Propagation Strategies

Case Study Overview

Phase III Oncology Trial

Q&A



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Background

Multiple Endpoints in Oncology

In many contemporary Phase III oncology programs, a single primary endpoint is no longer sufficient

- **Overall Survival (OS)** remains the gold standard
- But OS takes too long to mature leading to **very long and expensive** clinical trials

Sponsors frequently structure confirmatory trials with OS on top of an endpoint that is faster to measure

- **Progression-Free Survival (PFS)**
 - could support regulatory interaction earlier, potential accelerated approval
- **Overall Response Rate (ORR)**
 - could support early futility decision making to further save resources

Multiple Endpoints Considerations

- Correlation between endpoints
- Endpoints can mature at different rates
- Endpoints may be influenced by post-progression therapy, imaging frequency, and dropout patterns

Separate power computations for each endpoint do not suffice as we must understand how they **behave together**.

This is where **simulation** becomes essential to evaluate, for example

- using OS only, versus
- PFS & OS, versus
- ORR, PFS & OS as a combination of endpoints

to discuss tradeoffs of each approach and recommend how to develop trial programs.



Generating Patient Outcome Data

Simulating Oncology Trials

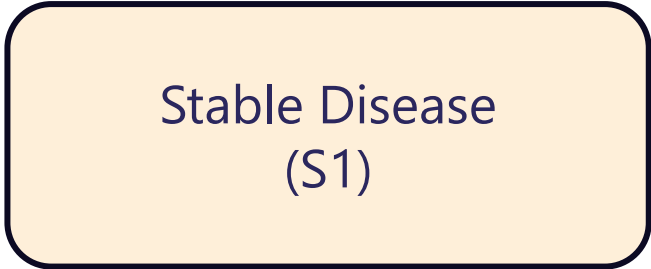
Data Generation Approaches

Multi State Models

- What are the states patients can be in
- How can patients move between states
- How can I estimate the relationship of moving between states
- What is the probability of moving from one state to another, while skipping a state

Data Generation Approaches

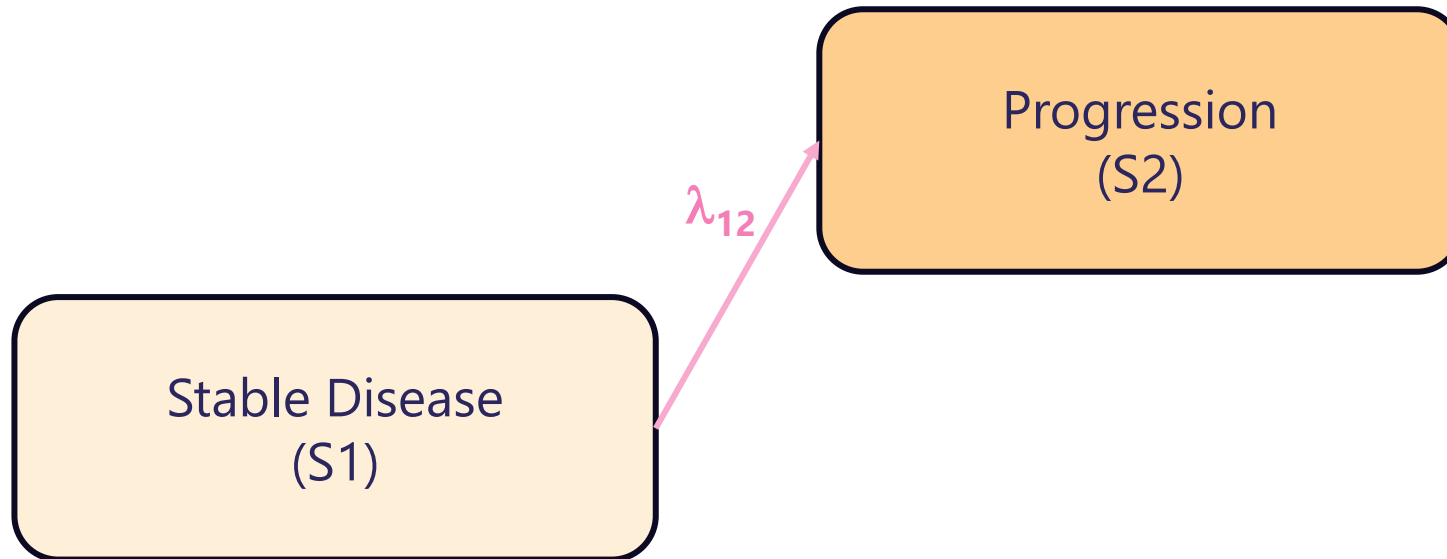
Two Endpoints: PFS & OS



Stable Disease
(S1)

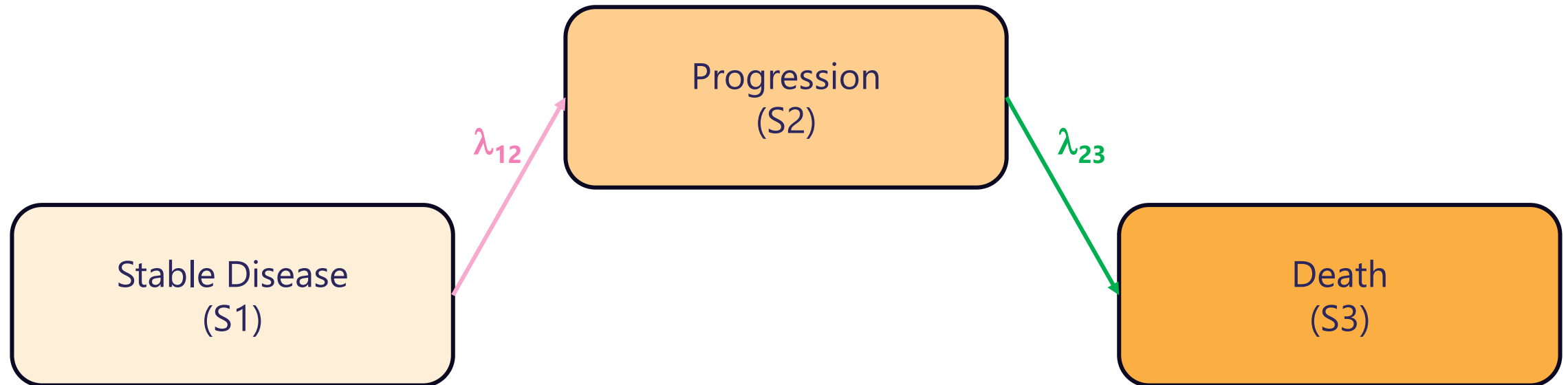
Data Generation Approaches

Two Endpoints: PFS & OS



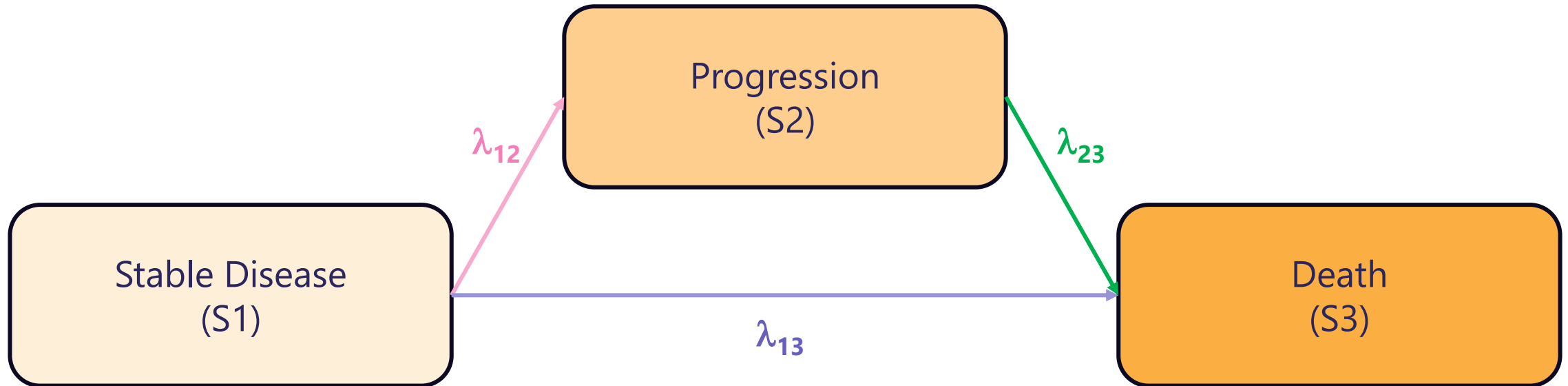
Data Generation Approaches

Two Endpoints: PFS & OS



Data Generation Approaches

Two Endpoints: PFS & OS



Must estimate λ_{12} , λ_{13} , λ_{23}

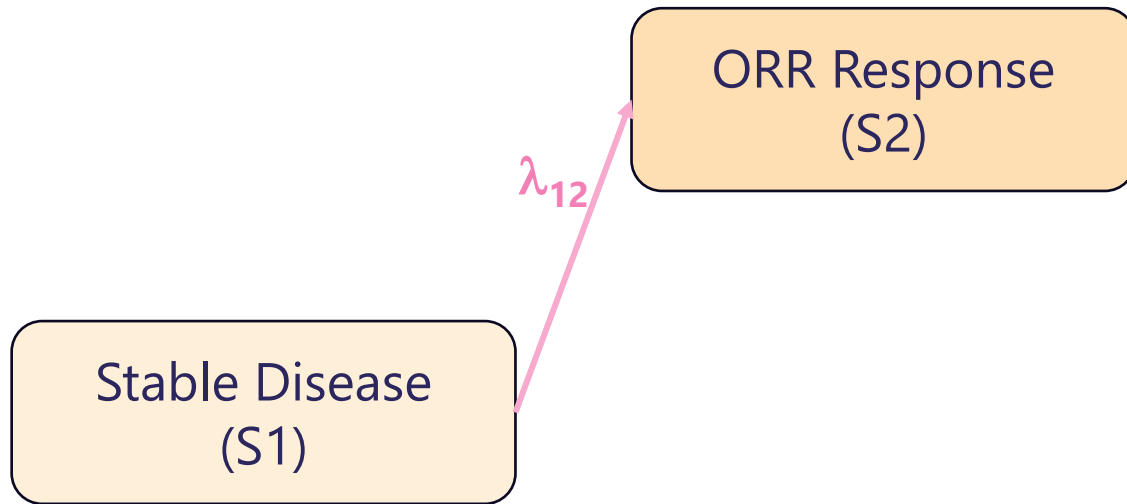
Data Generation Approaches

Three Endpoints: ORR & PFS & OS

Stable Disease
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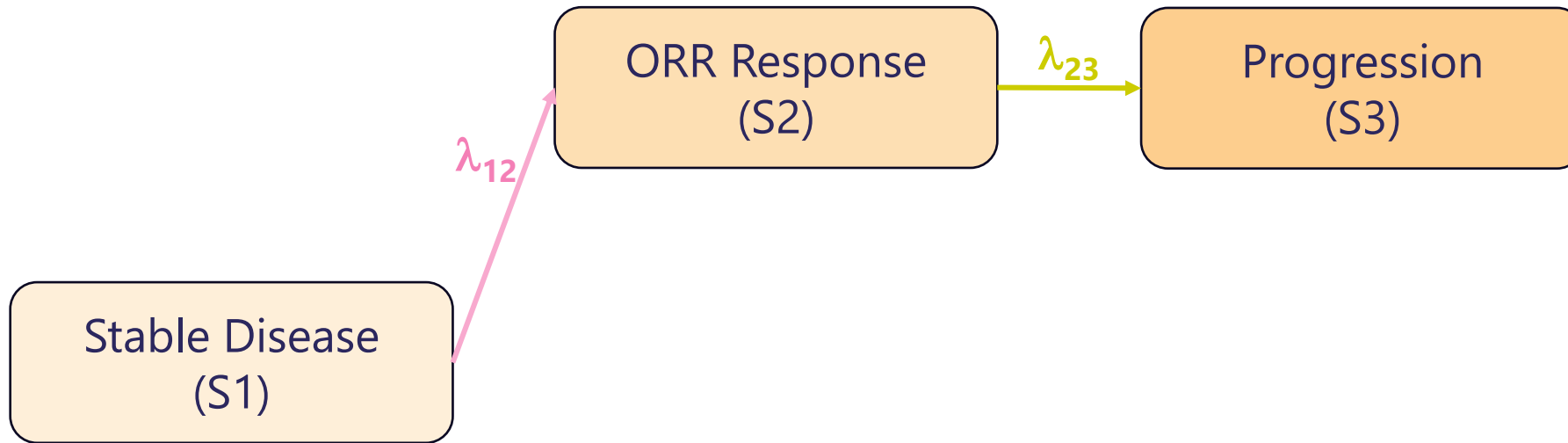
Data Generation Approaches

Three Endpoints: ORR & PFS & OS



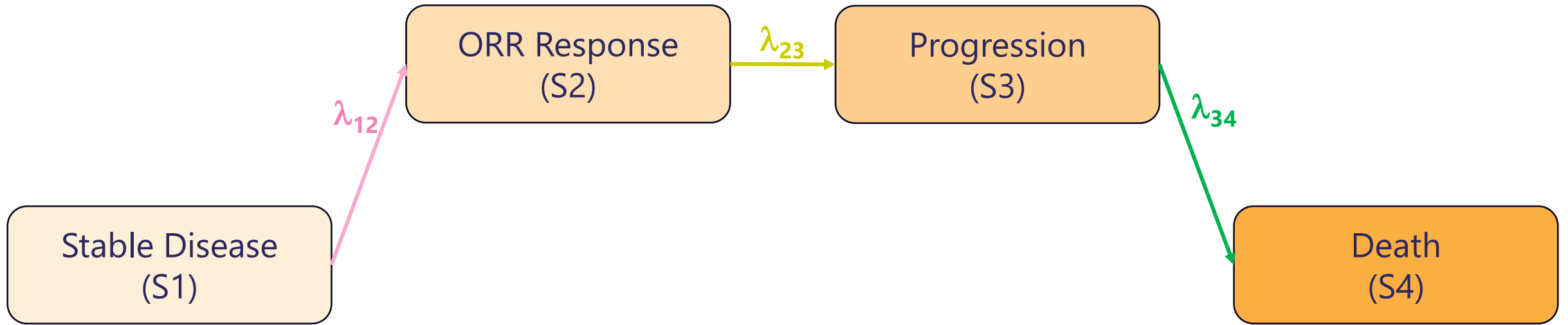
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Three Endpoints: ORR & PFS & OS



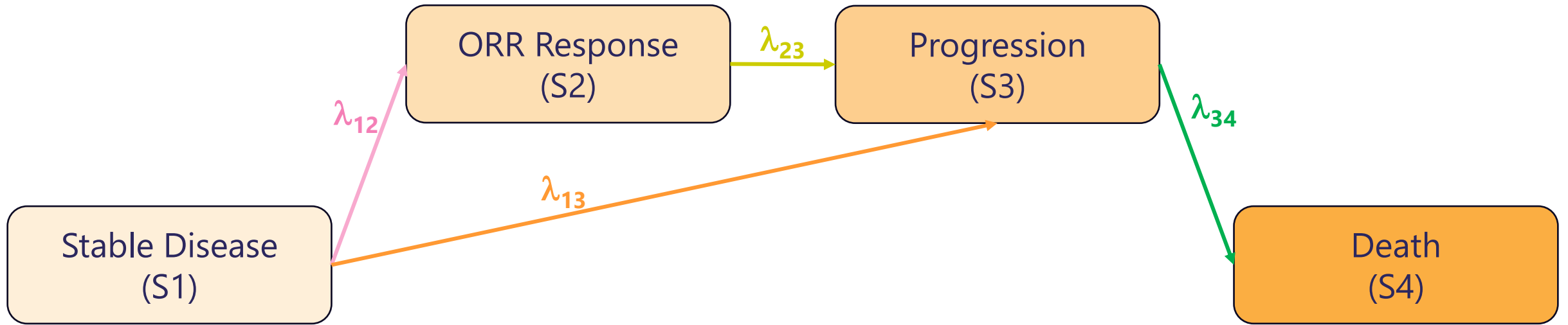
Data Generation Approaches

Three Endpoints: ORR & PFS & OS



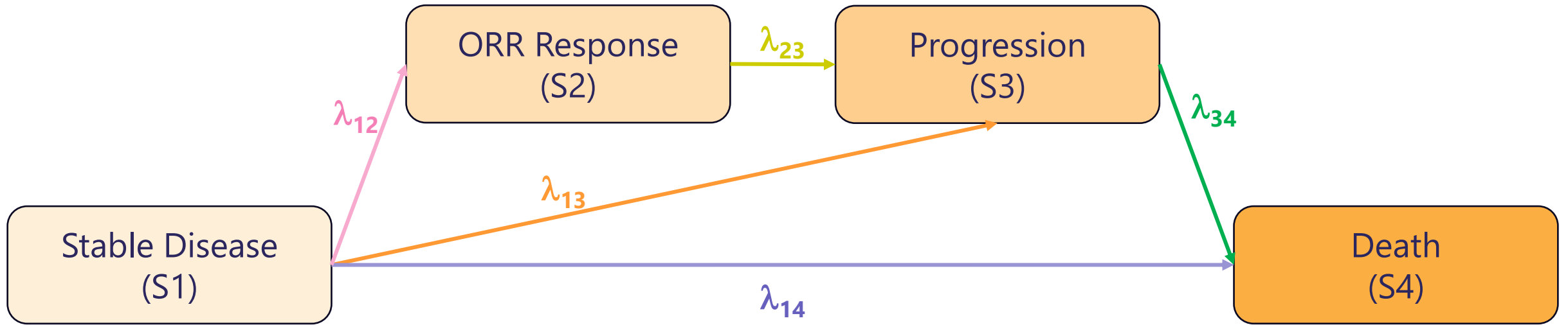
Data Generation Approaches

Three Endpoints: ORR & PFS & OS



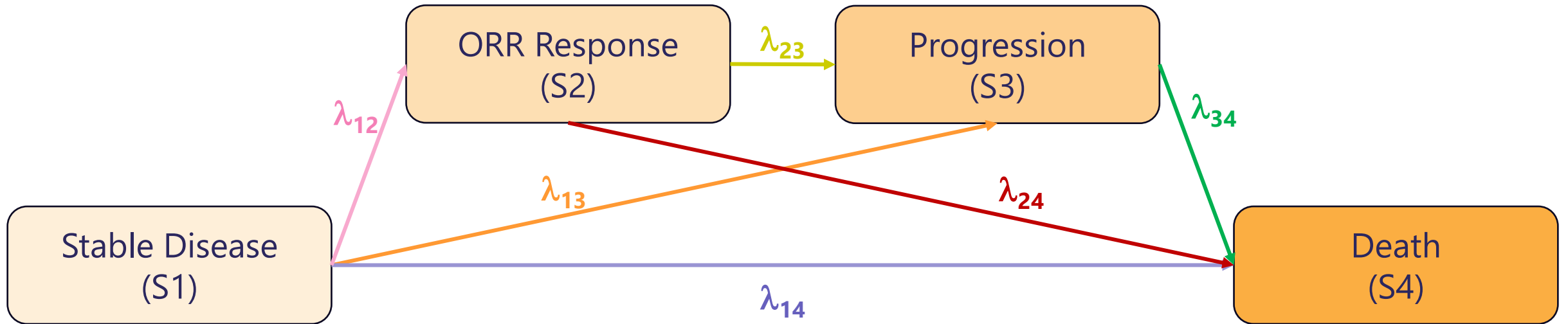
Data Generation Approaches

Three Endpoints: ORR & PFS & OS



Data Generation Approaches

Three Endpoints: ORR & PFS & OS



Must estimate λ_{12} , λ_{13} , λ_{14} , λ_{23} , λ_{24} , λ_{34}

Note: This is just ONE model, depending on disease, these can be even more complicated

Data Generation Approaches

Copula Method

- As models become more complicated, it also becomes difficult to estimate required parameters
- So often, simplifying assumptions get made
- E.g. correlation assumptions are easier to understand by non-statistician clinical peers

When doing this, you need **endpoint rules** to make sure it is possible

- e.g. PFS event cannot happen after OS event so in these cases, then consider PFS event time = OS event time

	ORR	PFS	OS
ORR	Perfectly + (1 to 1)	Moderate + (0.4 to 0.6) ▼	Weak + (0.2 to 0.4) ▼
PFS		Perfectly + (1 to 1)	Strong + (0.6 to 0.8) ▼
OS			Perfectly + (1 to 1)

Data Generation Approaches

- Additionally, correlation assumptions are easier to evaluate over **several** different versions of the assumptions because only one value needs to be modified for each relationship
- Recommendation is to simulate varying correlation matrices to then assess impact on the trial design operating characteristics
- Simulations can be built to simultaneously evaluate varying scenarios
- Best practice is to always include:
 1. Best guess, aka the **expected** correlation scenario
 2. A little bit **weaker** correlation between endpoints than expected
 3. A little bit **stronger** correlation between endpoints than expected

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Multiplicity Control

Controlling for Type-1 Error in Multiplicity Settings

P-Value-Based Single Step

- Bonferroni
- Weighted Bonferroni

P-Value-Based Stepwise

- Fallback
- Fixed Sequence
- Holms
- Weighted Bonferroni-Holms

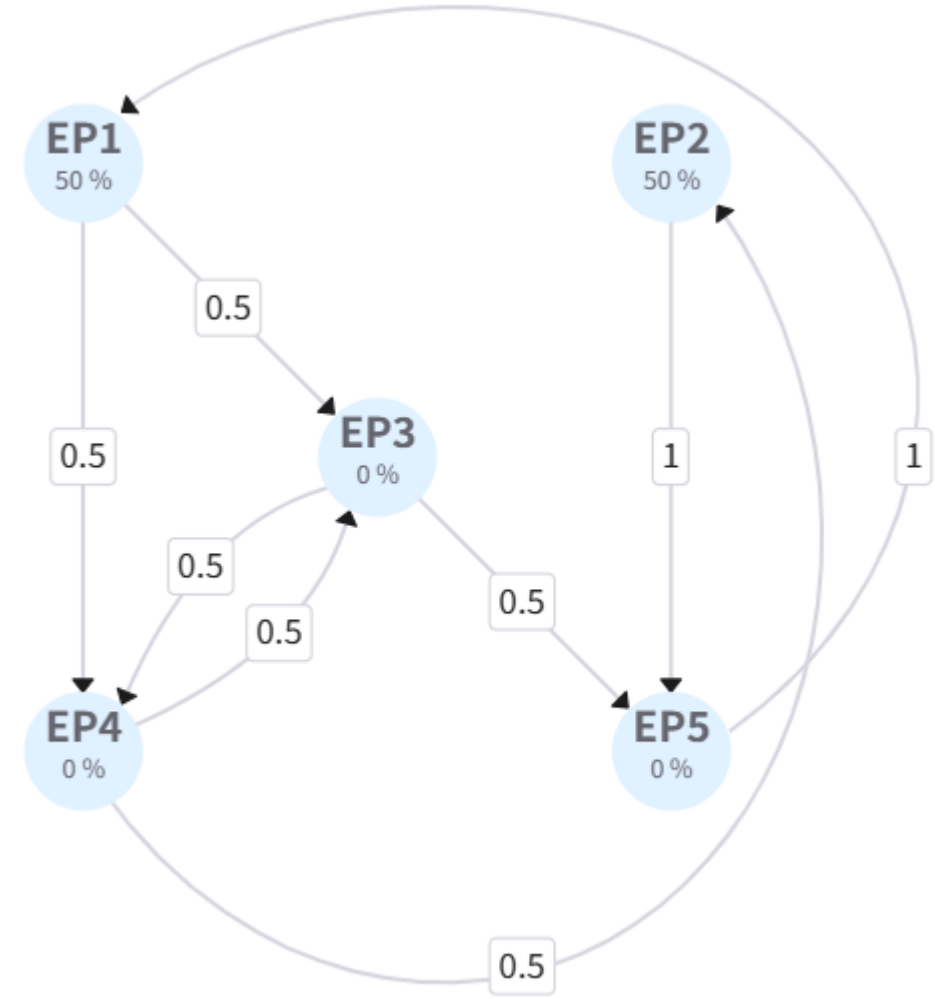
- Closed Testing procedures using P-value based single step tests can be computationally burdensome.
- Stepwise procedures help to alleviate this by acting as shortcuts while still preserving type-I error and maintaining high probability of study success.

Graphical Based Approach

More flexible approach for statisticians to have more control over alpha propagation strategy across endpoints and across analyses

Statisticians can choose how to

- assign initial alpha to each endpoints
- assign to recycle alpha from one endpoint to another, if test was significant
- assign how much and the direction(s) that alpha passes from one endpoint to another, if test was significant





Case Study Overview

Phase III Oncology Trial

Phase III Trial: Oncology

Parameter	Initial Inputs
Endpoints	ORR, PFS, OS
Planned Sample Size	1200 (1:1 randomization)
Planned Number of Events	PFS: 450 OS: 800
Winning Condition	Win on PFS and OS endpoints
Type-1 Error (1-sided)	2.5%
Analysis Plan	IA1: ORR IA2: PFS + OS FA : PFS + OS

Endpoint	Definition	Control	Experimental
ORR	Tumor reduction $\geq 20\%$ by 3 months	pC = 0.10	pE = 0.25
PFS	Progression of tumor	Median = 12 months	HR = 0.70
OS	Death from any cause	Median = 20 months	HR = 0.80

Interim Analysis Strategy

Interim Analysis 1

- ORR tested
- Timing determined by achieving 90-95% power for the ORR endpoint
- Information fraction 40% (i.e. 500 patients)

Interim Analysis 2

- PFS and OS tested
- Conducted when 60% of PFS events are observed (i.e. 270 events)

Final Analysis

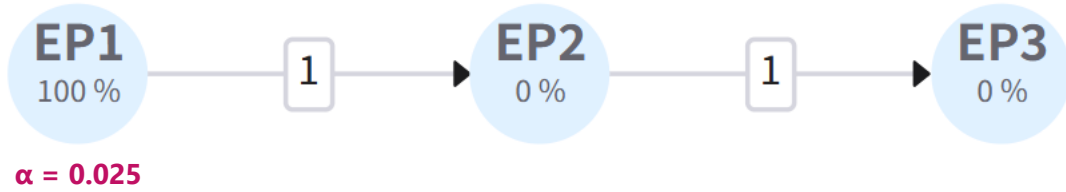
- PFS and OS tested
- Conducted at 100% of OS events (i.e. 800 events)

Alpha Propagation Strategies

EP1: ORR
EP2: PFS
EP3: OS

Option 1

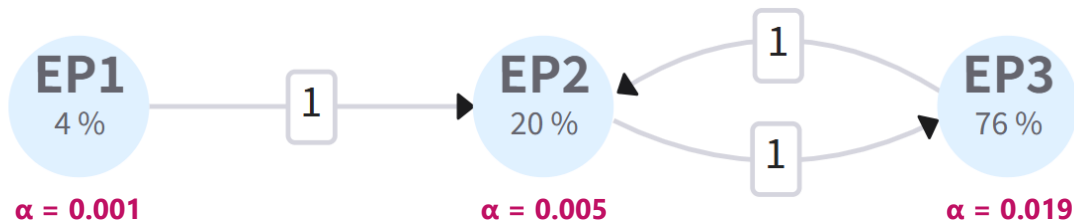
Simple, fixed sequence procedure



Test Order	Endpoint	Proportion of Alpha (%)	Alpha
... 1	ORR	100	0.025
... 2	PFS	0	0
... 3	OS	0	0

Option 2

More complex, more chance of winning on more "important" endpoints



Transition Matrix ⓘ				Proportion of Alpha (%)	Alpha
	EP1	EP2	EP3		
ORR	0	1	0	4	0.001
PFS	0	0	1	20	0.005
OS	0	1	0	76	0.019

Simulation Setup

Design 1

Fixed Sequence



Design 2

gMCP approach specified via transition matrix



Scenario 1:

Assume **high** success on ORR

- $\pi_C = 0.10$
- $\pi_E = 0.25$

Scenario 2:

Assume **low** success on ORR

- $\pi_C = 0.10$
- $\pi_E = 0.15$

2 designs * 2 ORR scenarios
= 4 simulation models

Correlation Variations

Scenario 1 (expected)	Scenario 2	Scenario 3
OS-PFS Strong	OS-PFS Weak	OS-PFS None
PFS-ORR Moderate	PFS-ORR Weak	PFS-ORR None
OS-ORR Weak	OS-ORR Weak	OS-ORR None

None = 0

Weak \approx 0.2-0.4

Moderate \approx 0.4-0.6

Strong \approx 0.8-1.0

**2 designs * 2 ORR scenarios * 3 correlation scenarios
= 12 simulation models**

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Results

Probability of Winning

Comparing Alpha Propagation Strategies

Design	ORR Scenario	Expected Correlation (Strong – Medium – Weak)
Fixed Sequence	High Treatment Effect	84.64 %
gMCP	High Treatment Effect	84.61 %
Fixed Sequence	Low Treatment Effect	33.72 %
gMCP	Low Treatment Effect	85.19 %

Probability of Winning

Comparing Correlation Assumptions (Expected Response)

Design	ORR Scenario	Correlation (Strong – Medium – Weak)	Correlation (Weak – Weak – Weak)	Correlation (None – None – None)
Fixed Sequence	High Treatment Effect	84.64 %	84.33 %	85.09 %
gMCP	High Treatment Effect	84.61 %	85.38 %	84.96 %

Probability of Winning Comparing Correlation Assumptions (Pessimistic Response)

Design	ORR Scenario	Correlation (Strong – Medium – Weak)	Correlation (Weak – Weak – Weak)	Correlation (None – None – None)
Fixed Sequence	Low Treatment Effect	33.72 %	34.18 %	32.48 %
gMCP	Low Treatment Effect	85.19 %	84.83 %	84.29 %

Probability of Winning – Summary

Design	ORR Scenario	Correlation (Strong – Medium – Weak)	Correlation (Weak – Weak – Weak)	Correlation (None – None – None)
Fixed Sequence	High Treatment Effect	84.64 %	84.33 %	85.09 %
gMCP	High Treatment Effect	84.61 %	85.38 %	84.96 %
Fixed Sequence	Low Treatment Effect	33.72 %	34.18 %	32.48 %
gMCP	Low Treatment Effect	85.19 %	84.83 %	84.29 %

*Reminder:
Overall Winning Condition
Win on PFS & OS*

Conclusions

Interim Analysis Timing

- ORR could have happened earlier to save time
- Simulations with IA1 evaluating ORR at 33% info, i.e. 400 patients, showed almost no impact on overall probability of winning

Alpha Propagation

- **Fixed sequence** test was not recommended for this case study
 - High drop in P(winning) when ORR assumption is incorrect
 - Low increase in P(winning) when ORR assumption is correct, so not very valuable anyways
- **Graphical approach** showed more robustness and flexibility as trials can claim success at least on PFS and OS even without ORR claim
 - Additionally, could increase the probability of winning by varying the success criteria to be "Winning on at least PFS or OS"

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Thank you!

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Appendix

Additional details if needed for Q&A

Calculating ORR completers ($\delta = 0.05$, $\alpha = 0.001$)

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.8
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.15
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.05
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	2690
Treatment (n_t)	1345
Control (n_c)	1345
Information (I)	6183.908
Sample sizes have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.85
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.15
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.05
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	2964
Treatment (n_t)	1482
Control (n_c)	1482
Information (I)	6813.793
Sample sizes have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.9
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.15
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.05
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	3326
Treatment (n_t)	1663
Control (n_c)	1663
Information (I)	7645.977
Sample sizes have been rounded.	

Total of 450 completers provides insufficient power to detect an effect size of $\delta = 0.05$

Calculating ORR completers ($\delta = 0.15$, $\alpha = 0.001$)

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.851
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.25
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.15
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	421
Treatment (n_t)	210
Control (n_c)	211
Information (I)	758.559
Sample sizes have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.9
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.25
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.15
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	472
Treatment (n_t)	236
Control (n_c)	236
Information (I)	850.45
Sample sizes have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Difference of Proportions (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.001
Power	0.95
Model	
Parameter	Value
Proportion Under Control (π_c)	0.1
Proportion Under Treatment (π_t)	0.25
$\delta = \pi_t - \pi_c$	
Under H0	0
Under H1	0.15
Allocation Ratio (n_t/n_c)	1
Variance	Unpooled Estimate
Casagrande-Pike-Smith Correction	Not Applied
Follow-up Time (Month)	0

Sample Size Information	
Parameter	Value
Sample Size (n)	554
Treatment (n_t)	277
Control (n_c)	277
Information (I)	998.198
Sample sizes have been rounded.	

500 completers selected to achieve 0.90-0.95 power

Calculating PFS events (HR = 0.7, $\alpha = 0.005$)

Design Summary																							
<table border="1"> <thead> <tr> <th>Parameter</th> <th>Value</th> </tr> </thead> <tbody> <tr> <td>Test Name</td> <td>Logrank Test Given Accrual Duration and Accrual Rates (Parallel Design)</td> </tr> <tr> <td>Hypothesis</td> <td>Superiority</td> </tr> <tr> <td>Test Type</td> <td>1-Sided</td> </tr> <tr> <td>Type 1 Error (α)</td> <td>0.005</td> </tr> <tr> <td>Power</td> <td>0.801</td> </tr> </tbody> </table>		Parameter	Value	Test Name	Logrank Test Given Accrual Duration and Accrual Rates (Parallel Design)	Hypothesis	Superiority	Test Type	1-Sided	Type 1 Error (α)	0.005	Power	0.801										
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450 PFS events selected to achieve 0.85-0.90 power

Calculating OS events (HR = 0.8, $\alpha = 0.019$)

Design Summary	
Test	
Parameter	Value
Test Name	Logrank Test Given Accrual Duration and Accrual Rates (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.019
Power	0.8
Model	
Parameter	Value
HR = λ_T/λ_C	
Under H0	1
Under H1	0.8
Survival Input Method	Median Survival Times
Median Survival Time (Control) (m_C) (Month)	20
Median Survival Times (Treatment: Alternative) (m_T) (Month)	25
Variance of Log Hazard Ratio	Null
Allocation Ratio (n_T/n_C)	1
Follow-up Time (Month)	Variable
Dropout	No

Sample Size Information	
Parameter	Value
Sample Size (n)	809
Treatment (n_T)	405
Control (n_C)	404
Events (s)	684
Treatment (s_T)	332
Control (s_C)	352
Information (I)	171
Sample sizes and events have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Logrank Test Given Accrual Duration and Accrual Rates (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.019
Power	0.85
Model	
Parameter	Value
HR = λ_T/λ_C	
Under H0	1
Under H1	0.8
Survival Input Method	Median Survival Times
Median Survival Time (Control) (m_C) (Month)	20
Median Survival Times (Treatment: Alternative) (m_T) (Month)	25
Variance of Log Hazard Ratio	Null
Allocation Ratio (n_T/n_C)	1
Follow-up Time (Month)	Variable
Dropout	No

Sample Size Information	
Parameter	Value
Sample Size (n)	904
Treatment (n_T)	453
Control (n_C)	451
Events (s)	778
Treatment (s_T)	378
Control (s_C)	400
Information (I)	194.5
Sample sizes and events have been rounded.	

Design Summary	
Test	
Parameter	Value
Test Name	Logrank Test Given Accrual Duration and Accrual Rates (Parallel Design)
Hypothesis	Superiority
Test Type	1-Sided
Type 1 Error (α)	0.019
Power	0.9
Model	
Parameter	Value
HR = λ_T/λ_C	
Under H0	1
Under H1	0.8
Survival Input Method	Median Survival Times
Median Survival Time (Control) (m_C) (Month)	20
Median Survival Times (Treatment: Alternative) (m_T) (Month)	25
Variance of Log Hazard Ratio	Null
Allocation Ratio (n_T/n_C)	1
Follow-up Time (Month)	Variable
Dropout	No

Sample Size Information	
Parameter	Value
Sample Size (n)	1033
Treatment (n_T)	517
Control (n_C)	516
Events (s)	905
Treatment (s_T)	442
Control (s_C)	463
Information (I)	226.25
Sample sizes and events have been rounded.	

800 OS events selected to achieve 0.85-0.90 power