A new approach to trial design and probabilistic risk assessment for trials with dual survival endpoints

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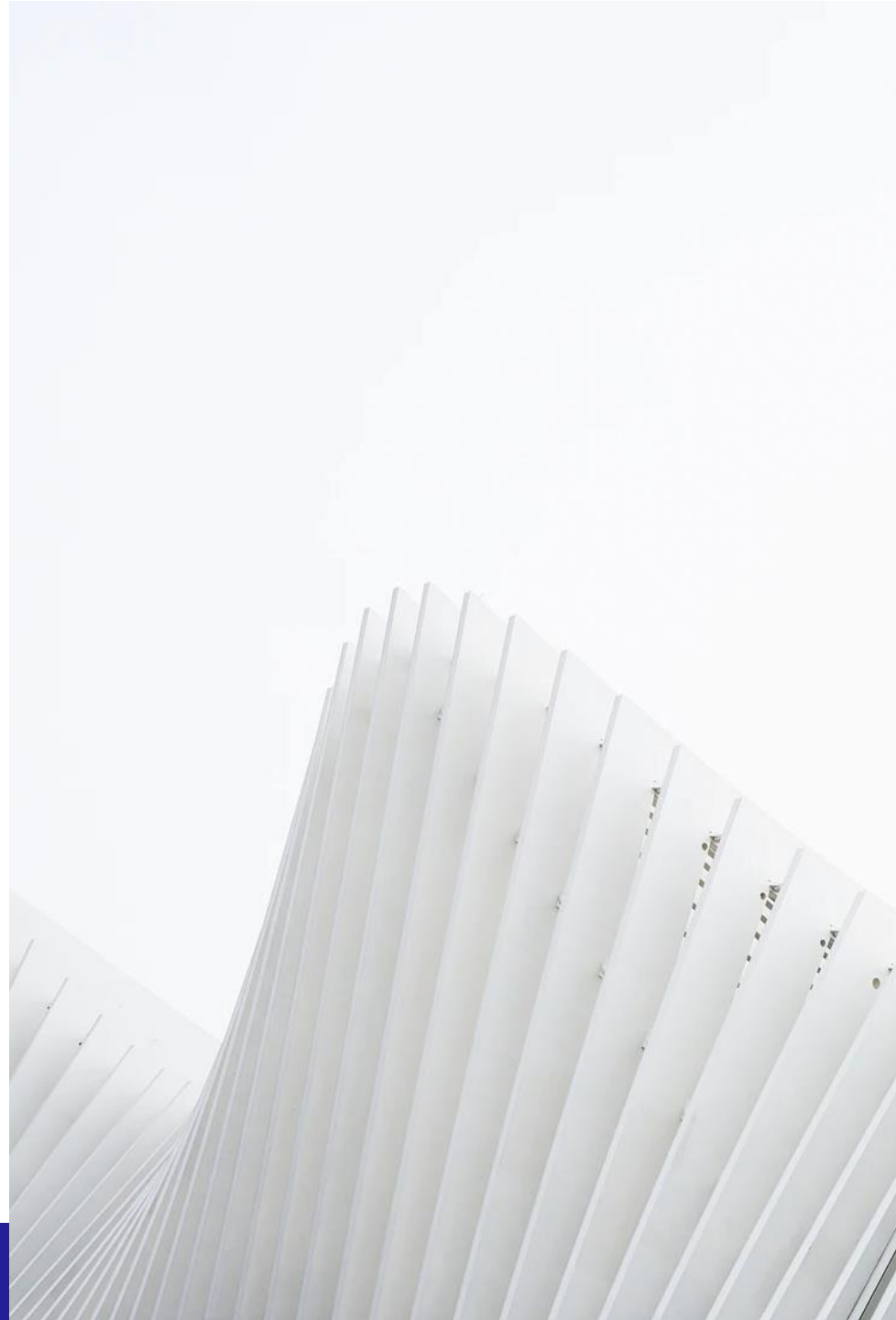
Agenda

- Motivation
- Dual TTE Endpoints: Logistics
- Case Study
- Q&A



Motivation

- Interim futility analysis with intermediate endpoints (Goldman, Leblanc and Crowley, 2008)
    - Futility testing commonly performed at very low levels (e.g., one-sided alpha 0.0025) at one or two times before final analysis.
- In TTE studies, problems might arise for adaptations, when using info on patients which are under risk at the interim. (Joergens, Wassmer et al, 2019)
    - Use Surrogate endpoints as basis for adaptations
- Systematic literature review to identify surrogate endpoints validated in oncology (Savina, PhD Thesis, 2018)

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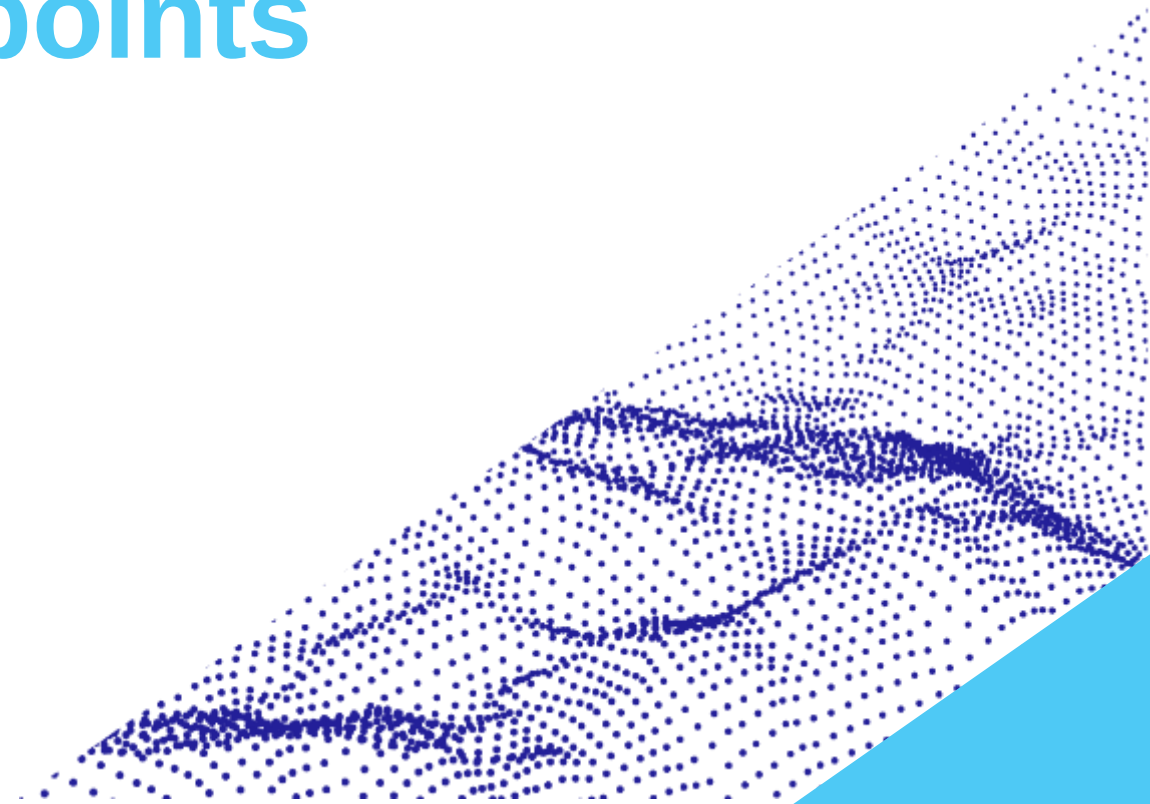
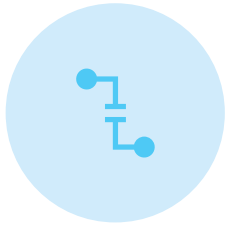
Designing for Two Endpoints



Key questions when designing trials with two endpoints

How do we define success?

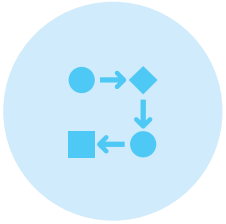


How do we specify correlation, or other relationships between endpoints?

In the absence of early stopping, when do we end the trial?

How do we adjust for multiple testing of hypotheses?

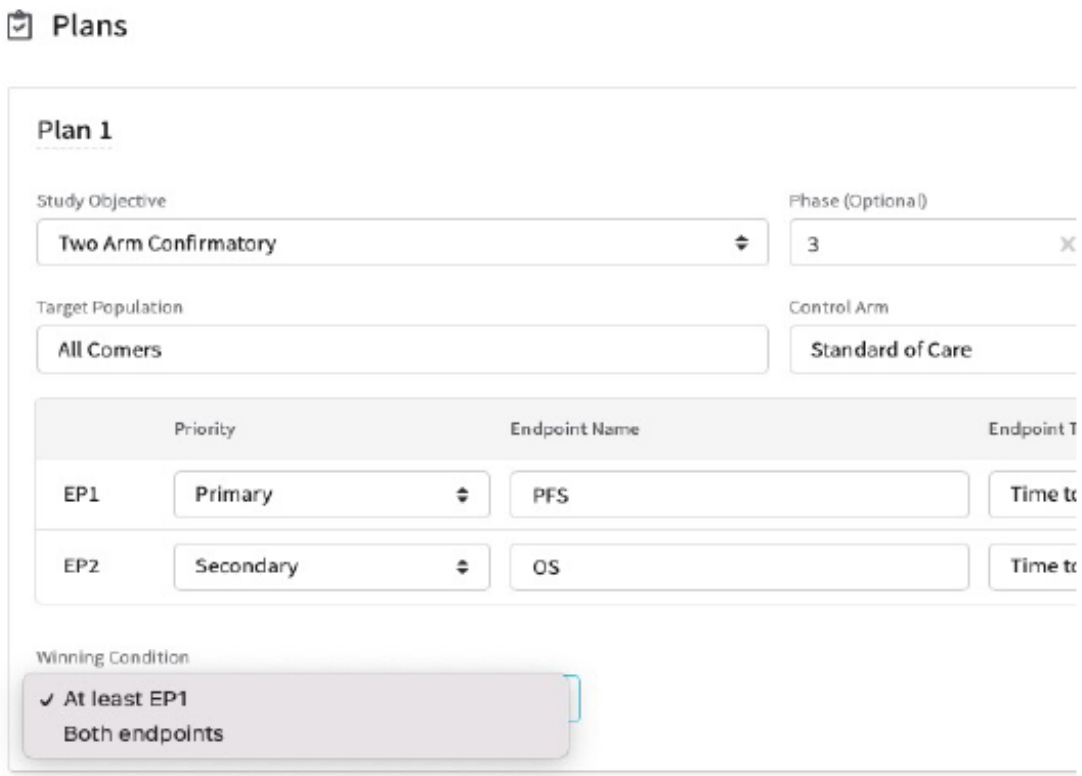
How is the timing of interim analyses determined?



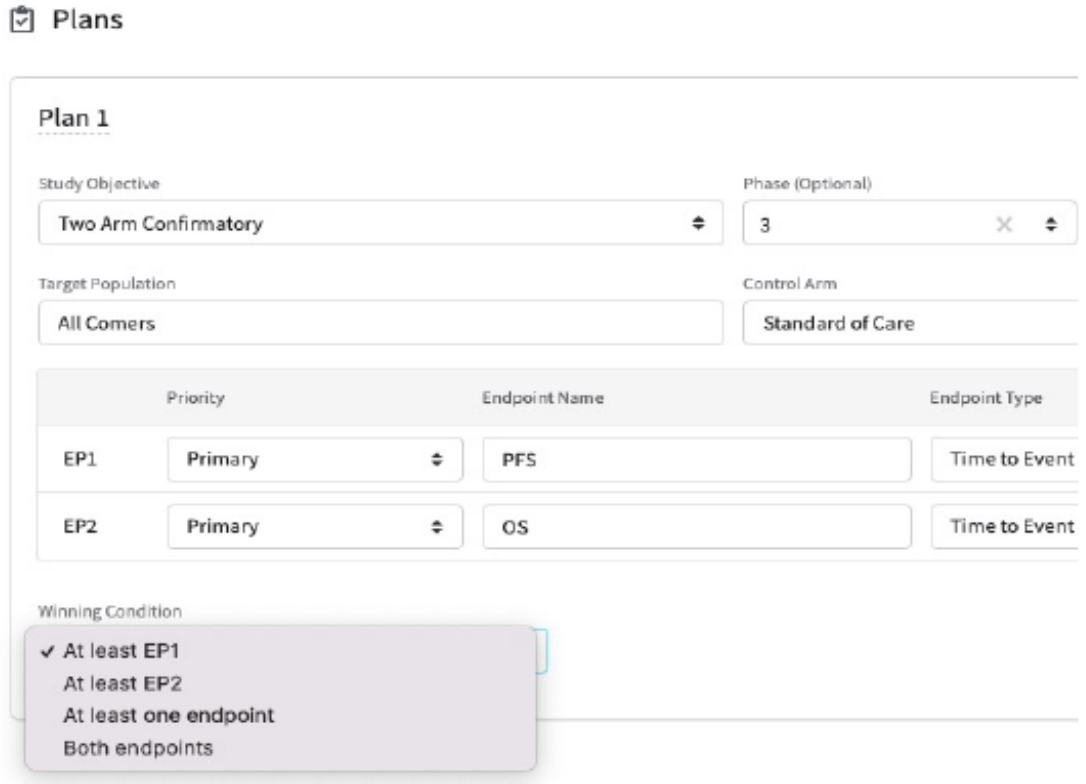
How do we define early stopping rules?

Designing a study with two endpoints (at least one TTE)

Primary + Secondary

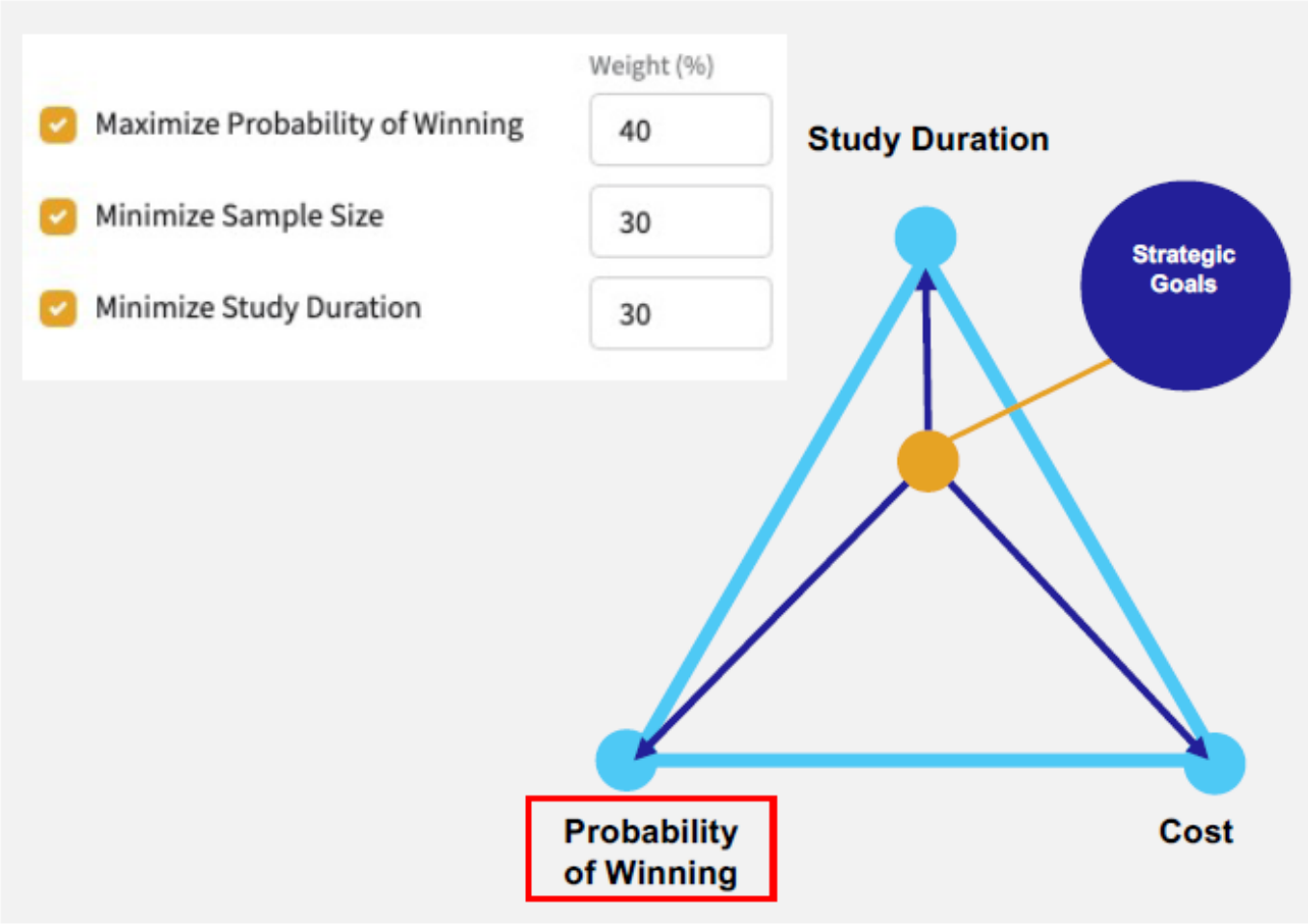


Primary + Primary



Power is no longer sufficient to define success when considering two endpoints.
Instead, Probability of Winning defines success based on the user-specified Winning Condition.

Scoring system uses Probability of Winning rather than Power



Models can be scored on performance criteria that reflect strategic goals

The score is a weighted scaled function of performance criteria

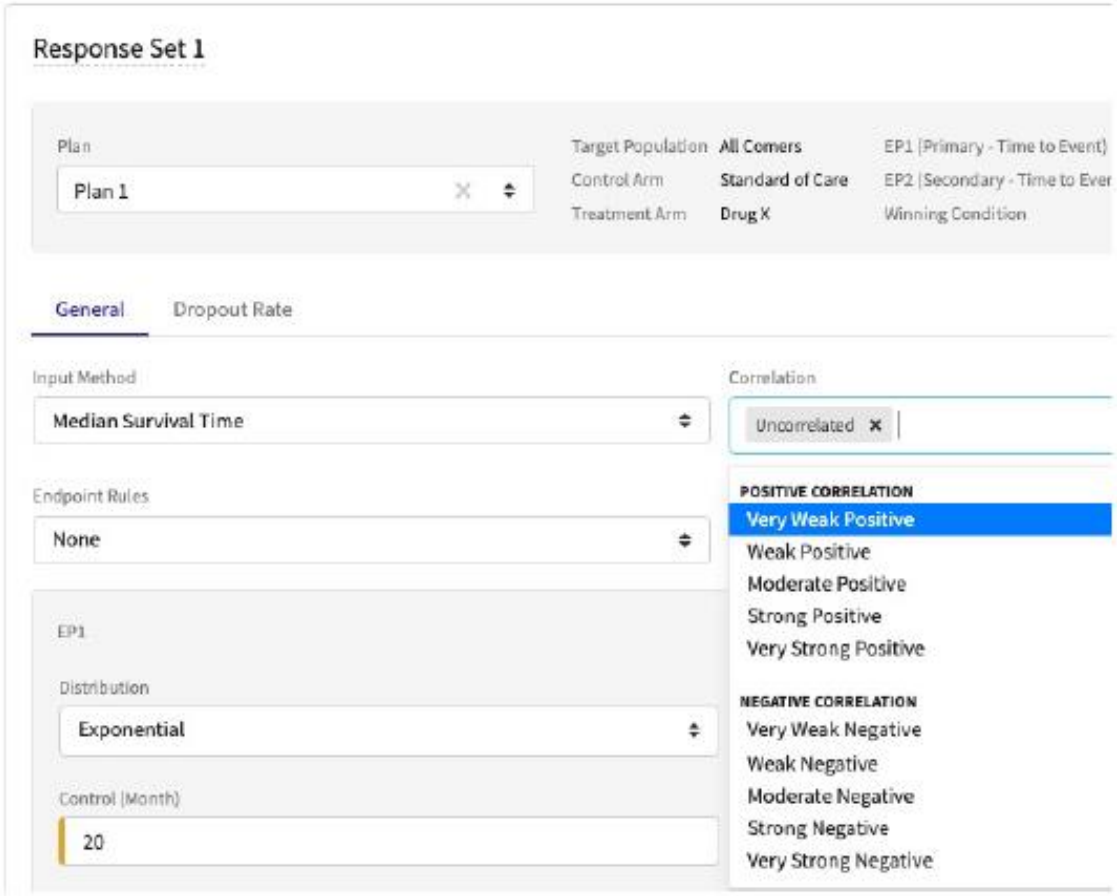
- Probability of Winning
- Study Duration
- Study Cost (or Sample Size)

Selecting general design-agnostic criteria enable broad strategic comparisons

Scoring is meant to surface areas of interest in the design map that merit further exploration

Generating Response Data

Correlated Endpoints



Generating Correlated Outcomes

Randomly generate two correlated random variables from a standard Bivariate Normal distribution with correlation qualitatively specified by the user:

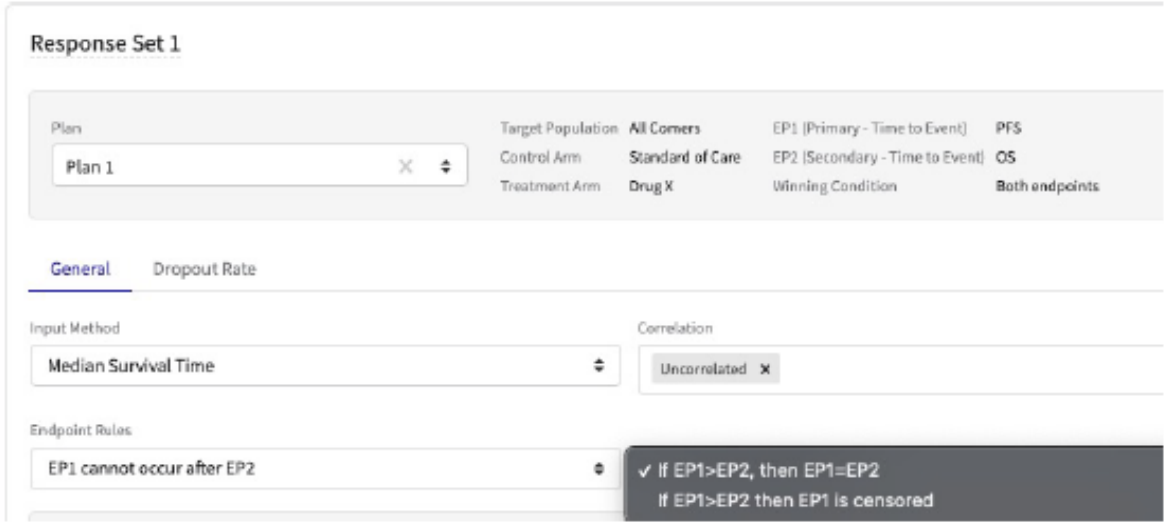
- **0:** Uncorrelated
- **+- 0.15:** Very Weak
- **+- 0.3:** Weak
- **+- 0.5:** Moderate
- **+- 0.7:** Strong
- **+- 0.85:** Very Strong

Using Cumulative Distribution Functions, transform – if necessary - the data to the desired distributions, exponential, piecewise exponential, binomial, etc.

Solara will report the actual observed correlation between the endpoints from simulation

Generating Response Data

Endpoint Rules



Dictating Logical Relationships

Some endpoints have logical relationships that dictate the order in which they will be observed for a subject, eg. PFS cannot occur after OS.

Other pairs of endpoints do not display this kind of relationship.

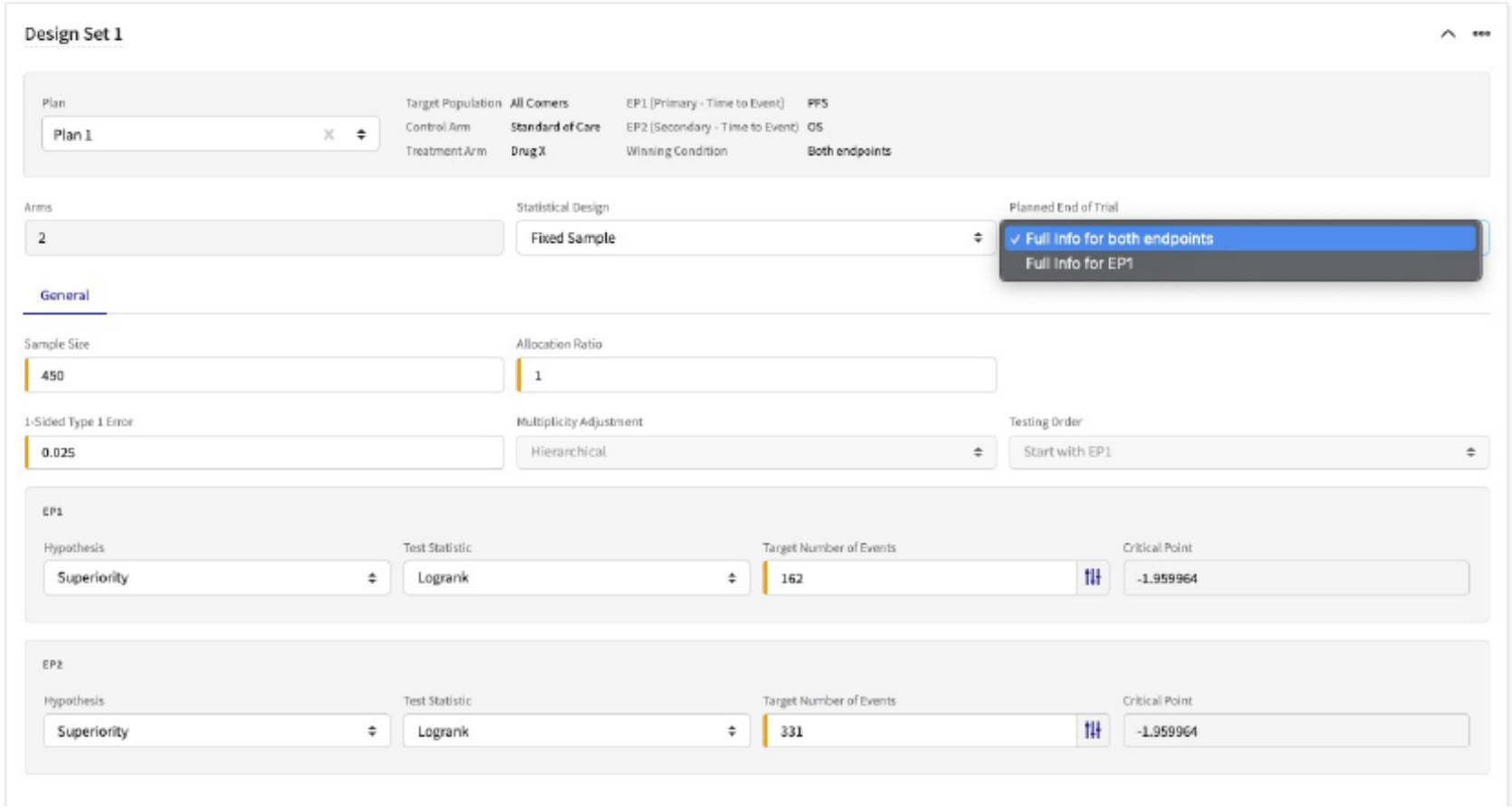
Solara needs to know this to generate the data appropriately.

It also needs to know what to do when such a violation occurs in the data generation process. There are two options:

- Count an event: Set the value of one endpoint to be the value of the other, eg. if a value of PFS time was generated that was large than the value of OS time, then PFS time = OS time
- Count a censoring event: The one endpoint is censored by the other, eg. Time to Progression if longer than Survival time would be censored by the time of death

Defining a Fixed Design

Primary + Secondary



Planned End of Trial

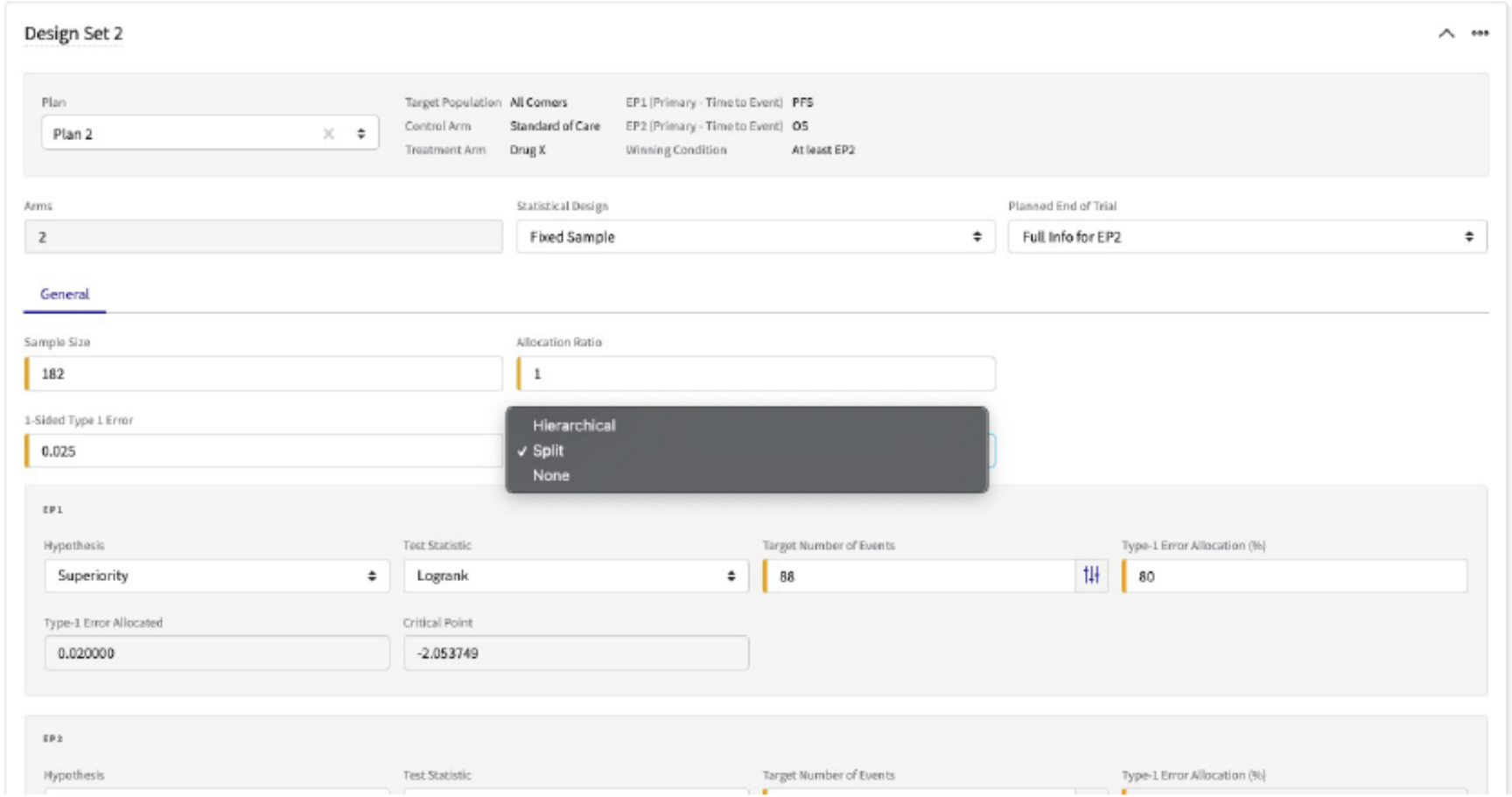
- Full info for EP1 (Primary)
- Full info for both endpoints

Multiplicity Adjustment options:

- Hierarchical:
  - Testing order is start with primary endpoint EP1

Defining a Fixed Design

Primary + Primary



Planned End of Trial

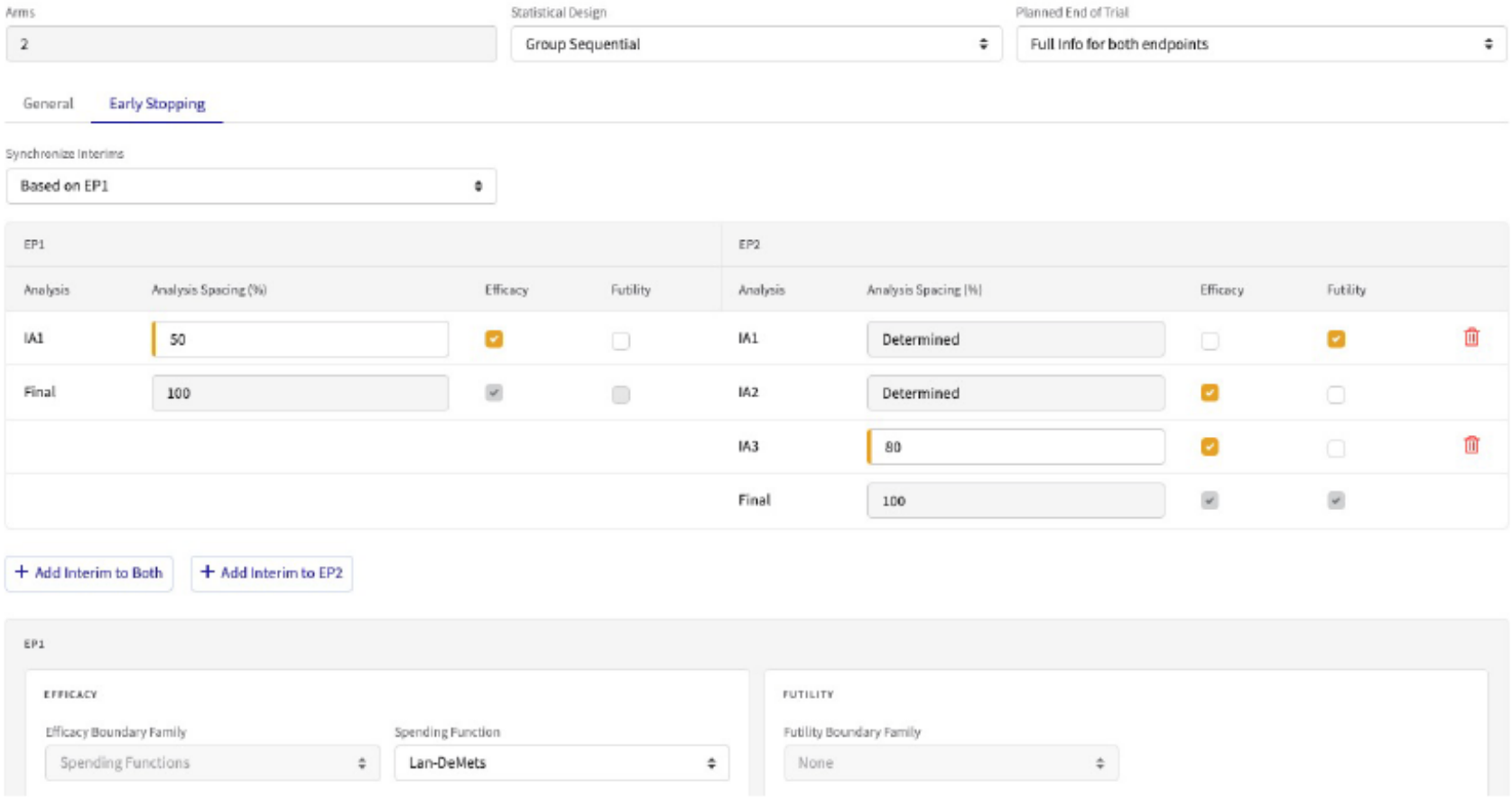
- Full info for EP1
- Full info for EP2
- Full info for both endpoints

Multiplicity Adjustment options:

- Hierarchical
  - Specify testing order
- Split : weighted Bonferroni
  - Specify allocation
- None

Defining a Group Sequential Design

Full info for both endpoints

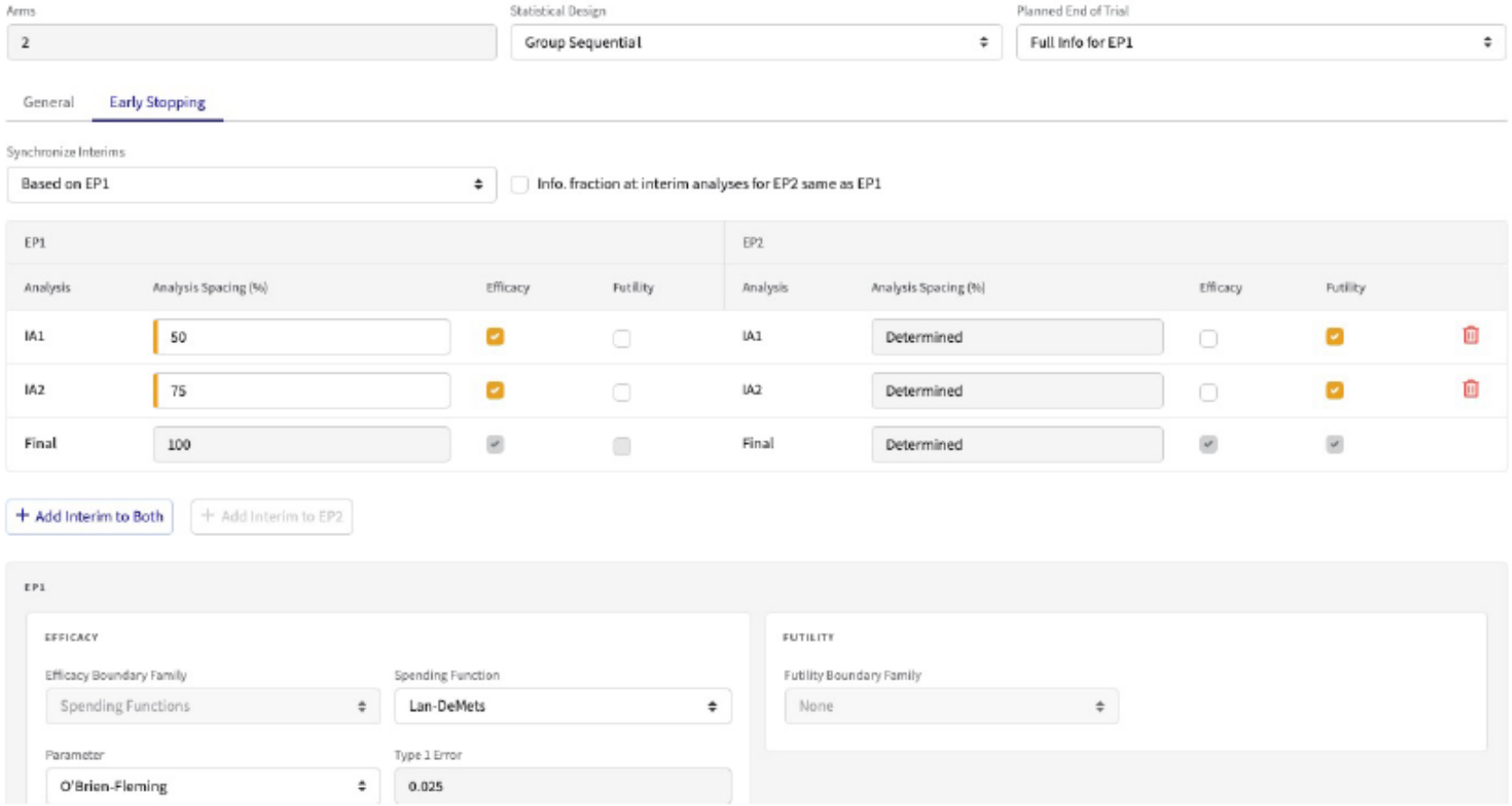


Synchronize interim analyses based on one of the endpoints

Information fraction for the other endpoint is determined during simulation with respect to the target number of events the user has specified

Defining a Group Sequential Design

Full info for driving endpoint

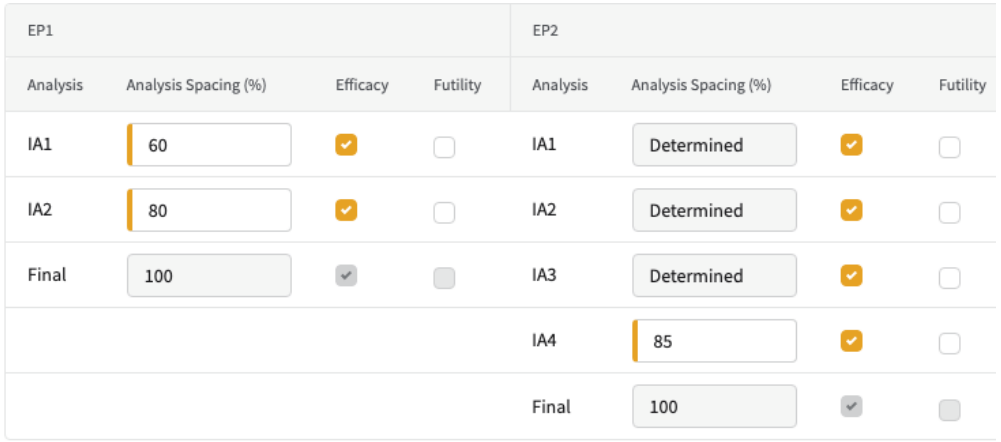


Synchronize interim analyses based on one of the endpoints

Information fraction for the other endpoint is determined during simulation with respect to the target number of events the user has specified OR equated to the information fraction for the synchronizing endpoint

Stopping Logic

- **Win on Both Endpoints / Hierarchical Testing**



EP1				EP2			
Analysis	Analysis Spacing (%)	Efficacy	Futility	Analysis	Analysis Spacing (%)	Efficacy	Futility
IA1	60	☑	☐	IA1	Determined	☑	☐
IA2	80	☑	☐	IA2	Determined	☑	☐
Final	100	☑	☐	IA3	Determined	☑	☐
				IA4	85	☑	☐
				Final	100	☑	☐

IA	PFS	OS	Decision
IA1	✓ Eff	✓ Eff	Win
IA1	✓ Eff	✗ Eff	Continue
IA1	✗ Eff		Continue

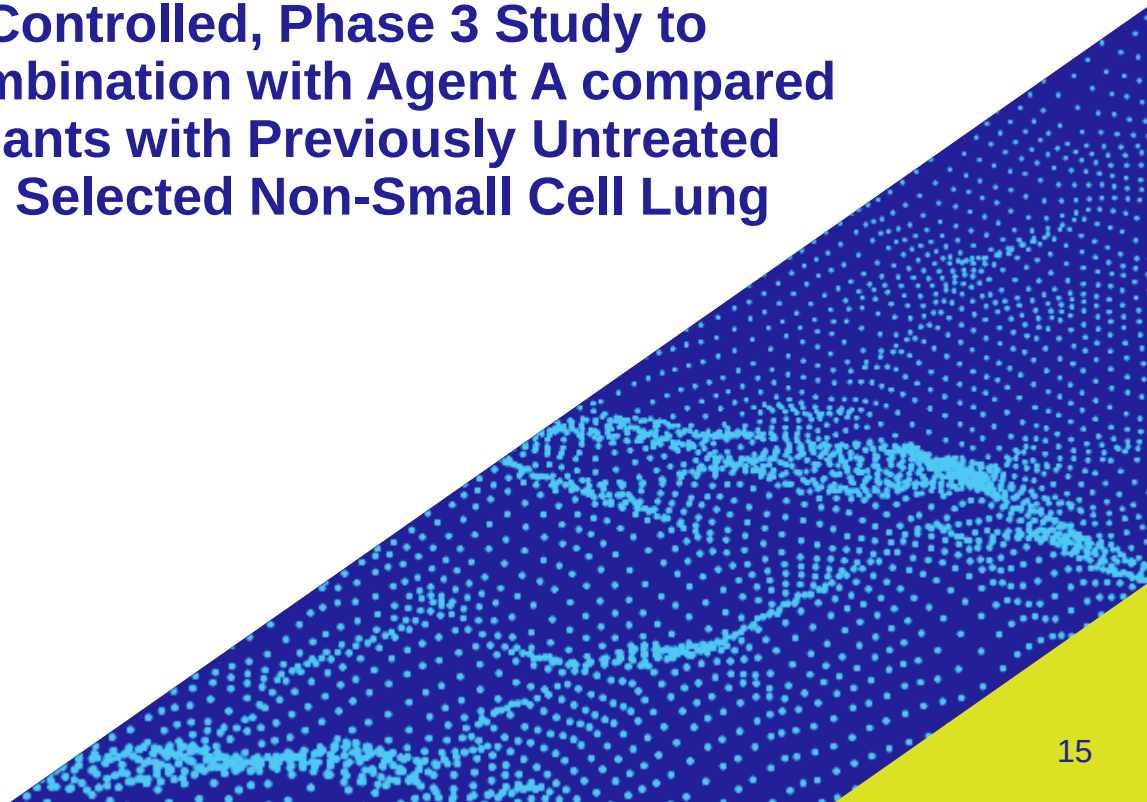
IA	PFS	OS	Decision
IA1	✗ Eff		Continue
IA2	✓ Eff	✗ Eff	Continue
FA/IA3		✓ Eff	Win
FA/IA3		✗ Eff	Continue

IA	PFS	OS	Decision
IA1	✗ Eff		Continue
IA2	✗ Eff		Continue
FA/IA3	✓ Eff	✓ Eff	Win
FA/IA3		✗ Eff	Continue

IA	PFS	OS	Decision
IA1	✗ Eff		Continue
IA2	✗ Eff		Continue
FA/IA3	✗ Eff		Lose

Case Study -

A Randomized, Multi-Center, Double-blind, Placebo Controlled, Phase 3 Study to Investigate Safety and Efficacy of Treatment X in combination with Agent A compared with Placebo in combination with Agent B in Participants with Previously Untreated Locally Advanced, Unresectable or Metastatic PD-L1 Selected Non-Small Cell Lung Cancer (NSCLC)



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Case Study 1 – ONCOLOGY/Lung

Parameter	Initial Inputs
Planned sample size	504
Number of events (if applicable)	328 for OS and 278 for PFS
Treatment/control effect	HR = 0.58 for PFS and HR=0.73 for OS
Standard deviation (if applicable)	
Follow-up time (if applicable)	
Allocation ratio	1:1
Type-1 error (1-sided)	0.1% for PFS and 2.4% for OS
Target average power	PFS: 92.7%, OS: 80%
Number of interim analyses (if applicable)	1 IA for PFS and 3 IA's for OS
Timing of interim analyses (if applicable)	PFS: 75% information OS: 32%, 50%, 75% information
Alpha spending function (if applicable)	Lan DeMets OBF boundaries
Promising zone minimum/maximum (if applicable)	
Target conditional power (if applicable)	
Beta spending function (if applicable)	

Exploration Goals

Primary Outcome –

Overall Survival

Progressions –free survival

Optimization Aim:

Other multiplicity approaches, Varying HR, varying information fraction, different data maturity for PFS/Final analysis, Probability of observing median in the active and control arms, critical values for HR (0.7 for PFS and 0.8 for OS)

Additional Information:

Time for primary analysis - recruitment +median of control arm

Accrual: 9 pts/m for first 6 m, 25 pts/m for 6-12 and 38 pts/m thereafter

mPFS = 6.9 m (curve plateaus – **piecewise exponential** with 50% at 6.9 m and 30% at 18 m), mOS = 22.2 (exponential curve)

Case Study 1 – ONCOLOGY/Lung – Simulation Plan

Parameter	Initial Inputs
Planned sample size	450, 504, 550
Number of events (OS)	255, 328, 390
Number of events (PFS)	230, 278, 310
Treatment/control effect (OS)	0.7, 0.73, 0.75
Treatment/control effect (PFS)	0.55, 0.58, 0.6
mPFS	6.9 months
mOS	22.2 months
Enrollment	9 pts/m for first 6 m, 25 pts/m for 6-12 and 38 pts/m thereafter
Allocation ratio	1:1
Type-1 error (1-sided)	0.1% for PFS and 2.4% for OS
Target average power	PFS: 92.7%, OS: 80%
Number of interim analyses	1 IA for PFS and 3 IA's for OS
Timing of interim analyses (PFS)	60%, 70%, 75%
Timing of interim analyses (OS)	(*, *, 75%), (*, *, 60%) *:determined
Alpha spending function (if applicable)	Gamma (-2, -3, -4)
Beta spending function (if applicable)	Gamma (-40, -4)
Total Models	48,440

Exploration Goals

Primary Outcome –

Overall Survival

Progressions –free survival

Optimization Aim:

Other multiplicity approaches, Varying HR, varying information fraction, different data maturity for PFS/Final analysis, Probability of observing median in the active and control arms, critical values for HR (0.7 for PFS and 0.8 for OS)

Additional Information:

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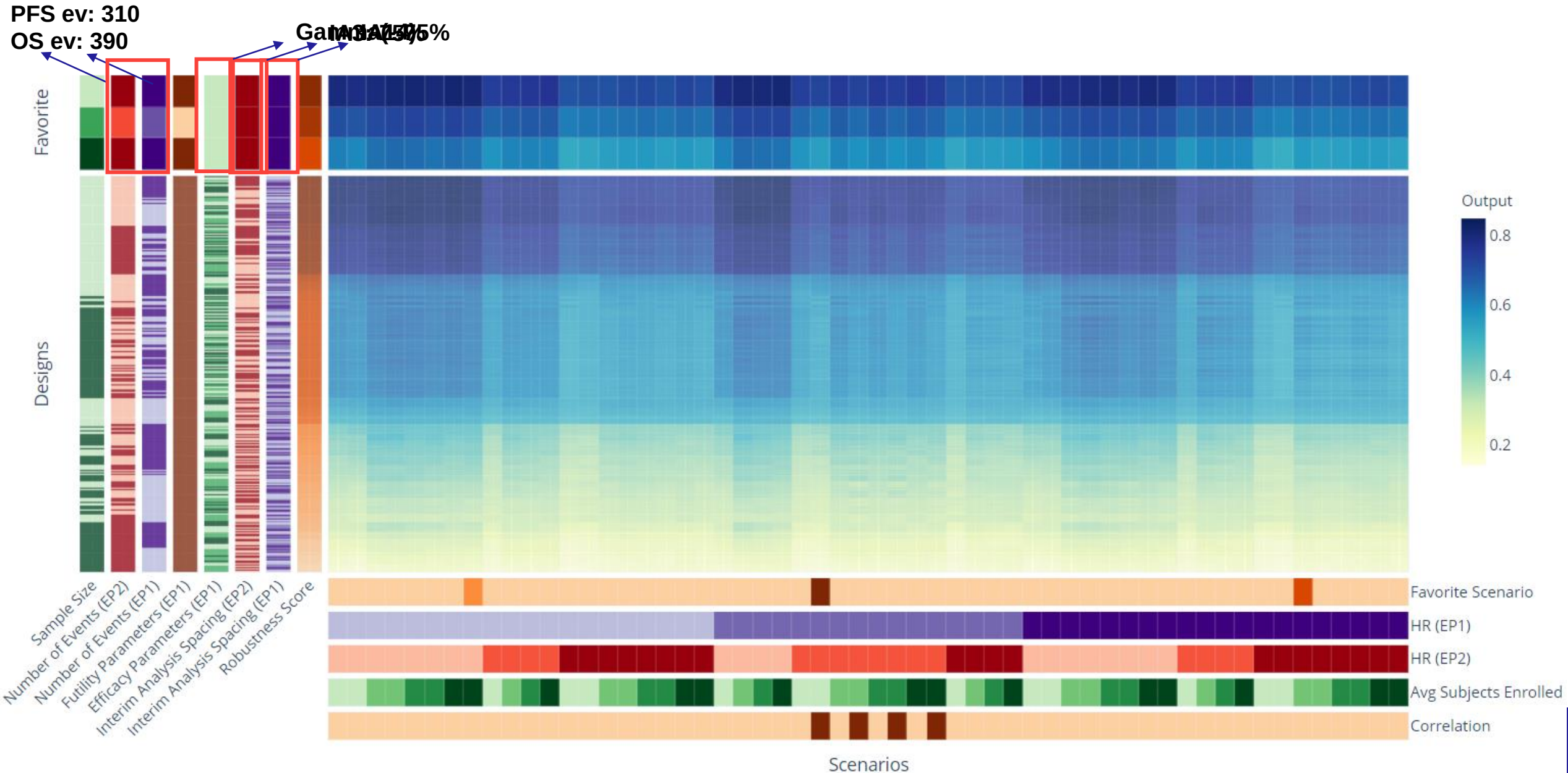
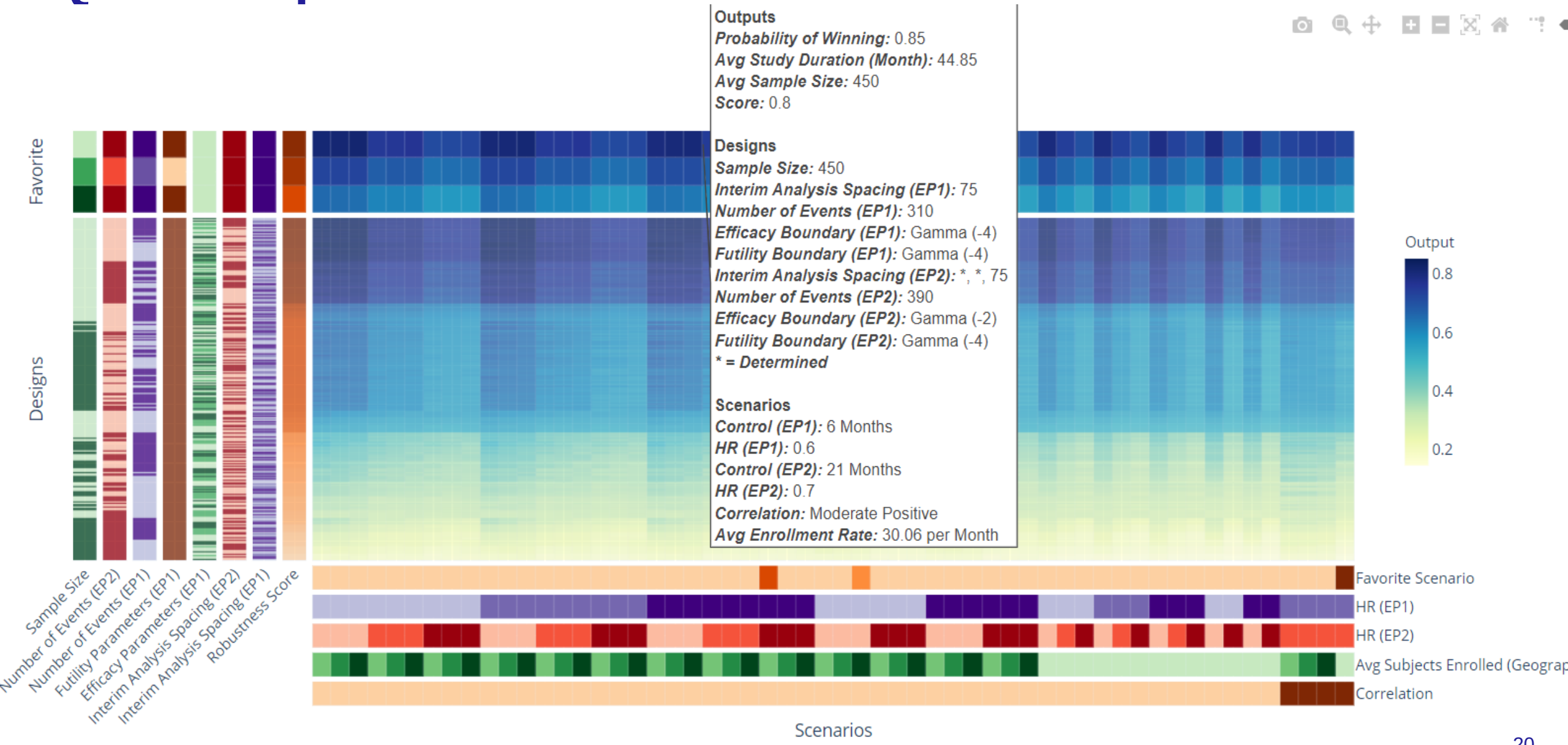
mPFS = 6.9 m (curve plateaus – **piecewise exponential** with 50% at 6.9 m and 30% at 18 m), mOS = 22.2 (exponential curve)

Exploring the Output

48440 Models = 865 Designs x 56 Scenarios



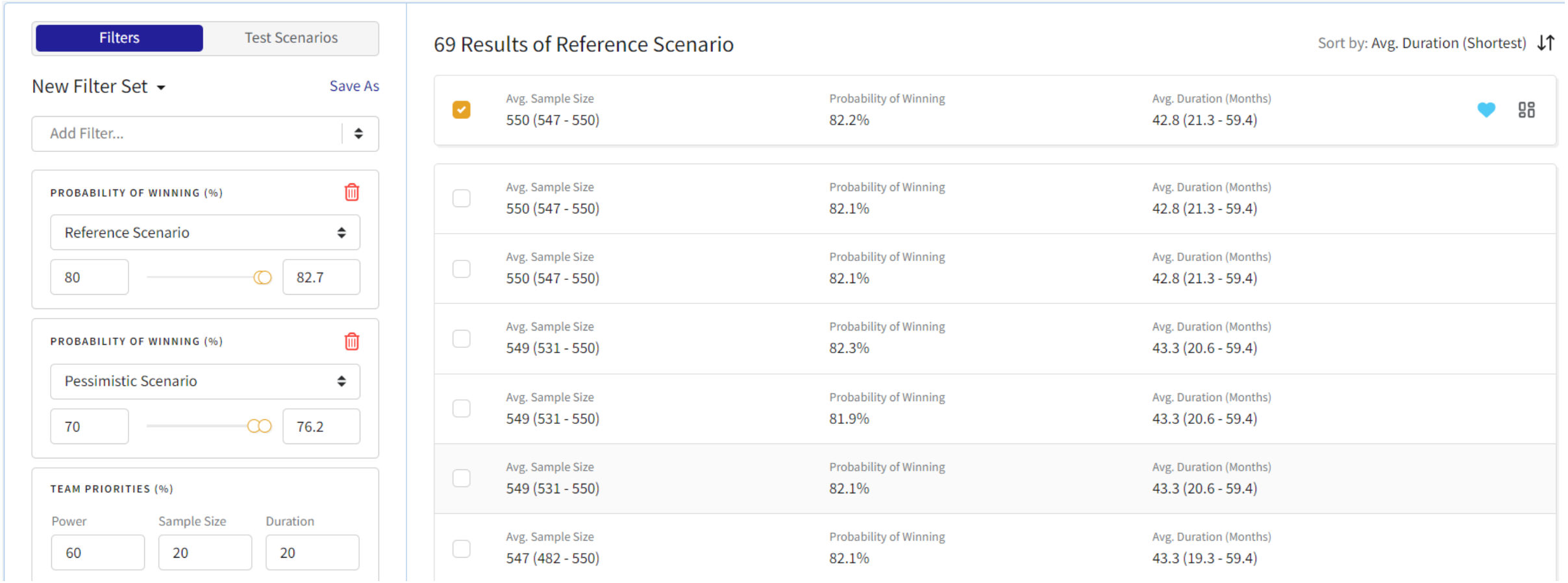
Quick output



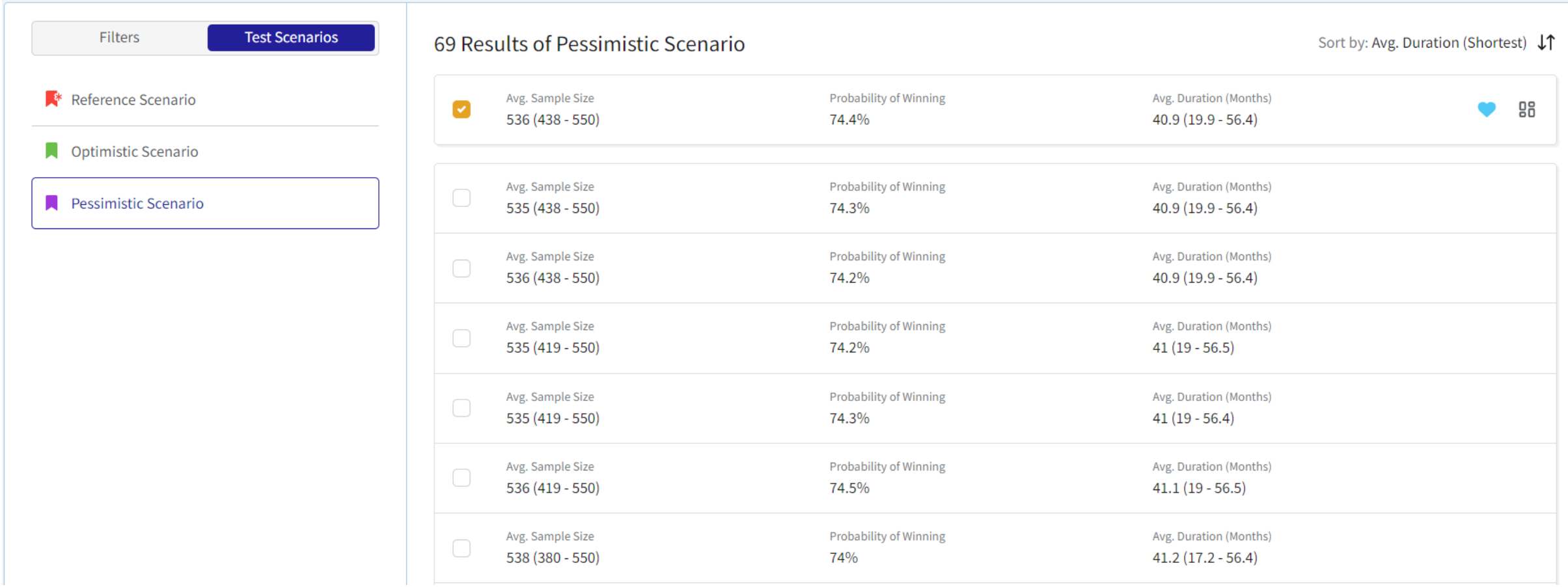
Tabular summary- Favorite Designs

Designs	AtLeast80PowerShort (Target Number of Events (EP1)=310;Target Number of Events (EP2)=390;Sample Size=550;Multiplicity Adjustment=Split;Analysis Spacing (%) Info (EP1)=[75];Analysis Spacing (%) Info (EP2)=["determined","determined",75];Efficacy Parameter (EP1)=-4;Futility Parameter (EP1)=-4)			AtLeast80PowerSmallN (Target Number of Events (EP1)=310;Target Number of Events (EP2)=390;Sample Size=450;Multiplicity Adjustment=Split;Analysis Spacing (%) Info (EP1)=[75];Analysis Spacing (%) Info (EP2)=["determined","determined",75];Efficacy Parameter (EP1)=-4;Futility Parameter (EP1)=-4)			Reference Design (Target Number of Events (EP1)=278;Target Number of Events (EP2)=328;Sample Size=504;Multiplicity Adjustment=Split;Analysis Spacing (%) Info (EP1)=[75];Analysis Spacing (%) Info (EP2)=["determined","determined",75];Efficacy Parameter (EP1)=-4;Futility Parameter (EP1)=N/A)		
Scenarios	Optimistic Scenario (HR (EP1)=0.55;HR (EP2)=0.7;Avg Subjects Enrolled=30)	Pessimistic Scenario (HR (EP1)=0.6;HR (EP2)=0.75;Avg Subjects Enrolled=22)	Reference Scenario (HR (EP1)=0.58;HR (EP2)=0.73;Avg Subjects Enrolled=9,25,38)	Optimistic Scenario (HR (EP1)=0.55;HR (EP2)=0.7;Avg Subjects Enrolled=30)	Pessimistic Scenario (HR (EP1)=0.6;HR (EP2)=0.75;Avg Subjects Enrolled=22)	Reference Scenario (HR (EP1)=0.58;HR (EP2)=0.73;Avg Subjects Enrolled=9,25,38)	Optimistic Scenario (HR (EP1)=0.55;HR (EP2)=0.7;Avg Subjects Enrolled=30)	Pessimistic Scenario (HR (EP1)=0.6;HR (EP2)=0.75;Avg Subjects Enrolled=22)	Reference Scenario (HR (EP1)=0.58;HR (EP2)=0.73;Avg Subjects Enrolled=9,25,38)
Outputs									
Average Probability Of Winning	0.933	0.744	0.822	0.909	0.716	0.8	0.863	0.679	0.741
Average Sample Size (Overall)	546.359	535.415	549.578	450	448.034	450	503.066	497.349	503.968
Average Number of Events (EP1) (Overall)	241.547	254.483	249.093	241.47	253.79	248.477	219.626	233.564	227.975
Average Number of Events (EP2) (Overall)	274.517	286.12	283.238	276.462	287.754	285.52	257.078	261.488	262.569
Average Study Duration (Month)	37.638	40.937	42.763	49.452	52.546	55.64	37.102	39.093	41.889
Average Accrual Duration (Month)	18.178	24.291	21.07	14.968	20.318	18.448	16.736	22.555	19.868

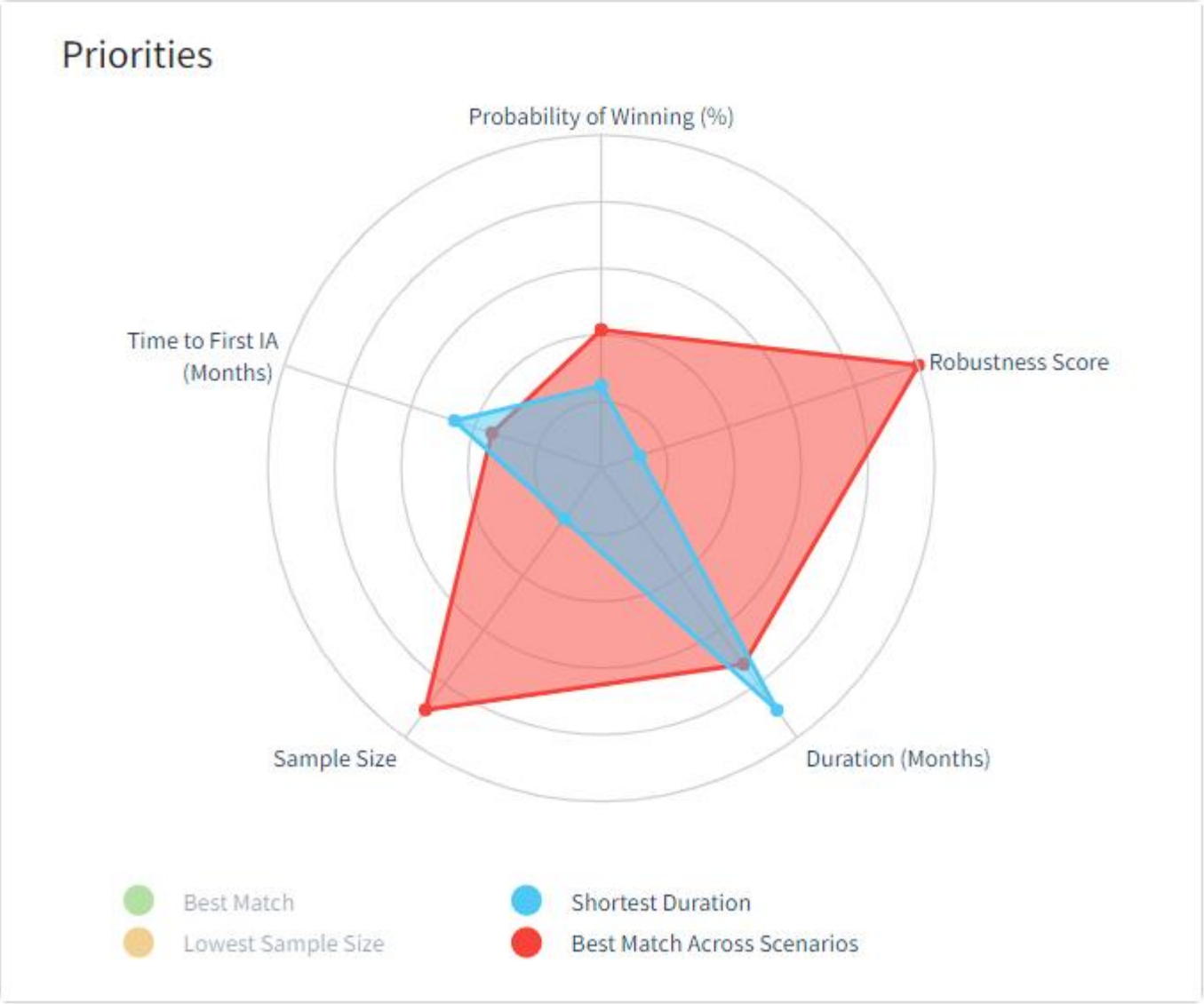
Optimizing Further



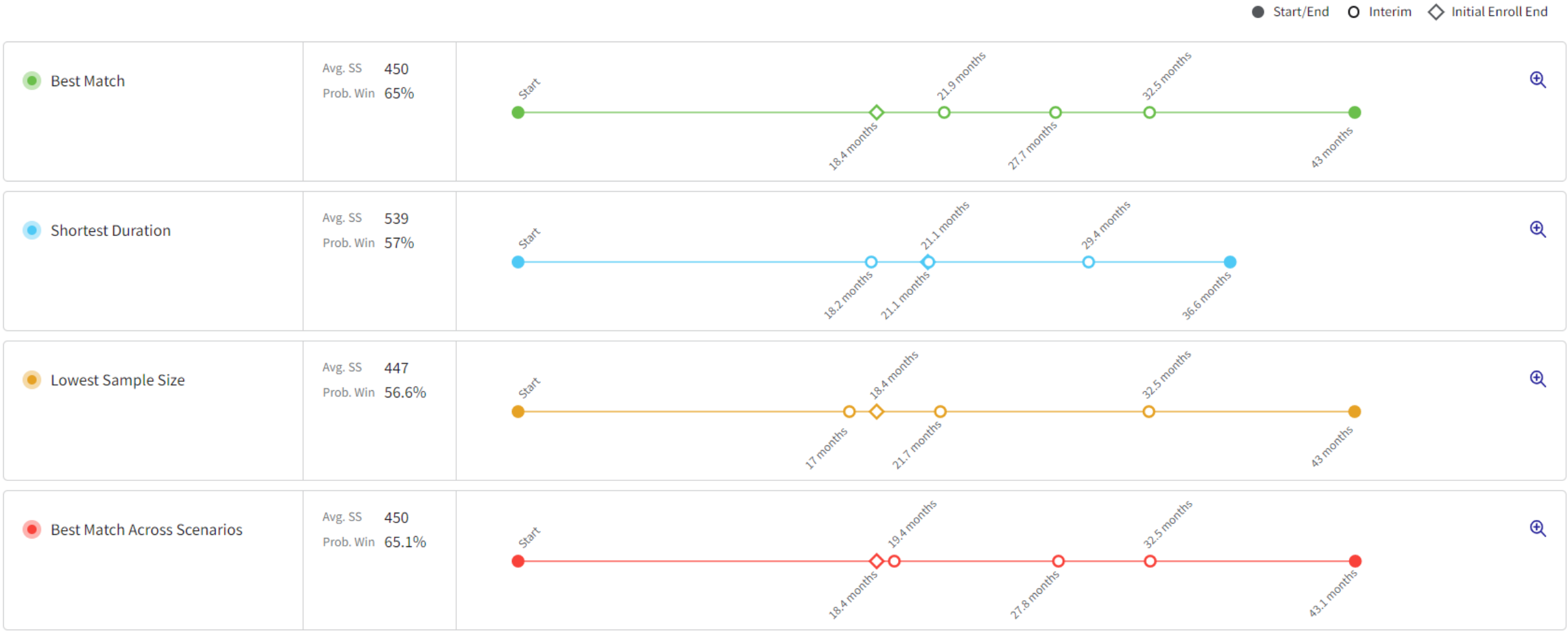
Under Pessimistic Scenario



Graphical Summaries: Radar Plot



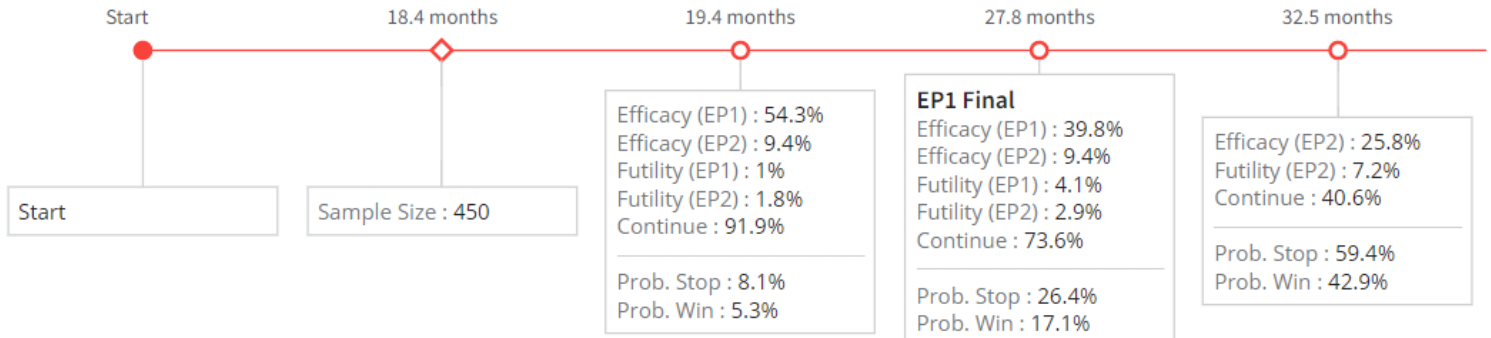
Timelines Comparison



Detailed Timelines per Design

Best Match Across Scenarios

Avg. SS 450
Prob. Win 65.1%



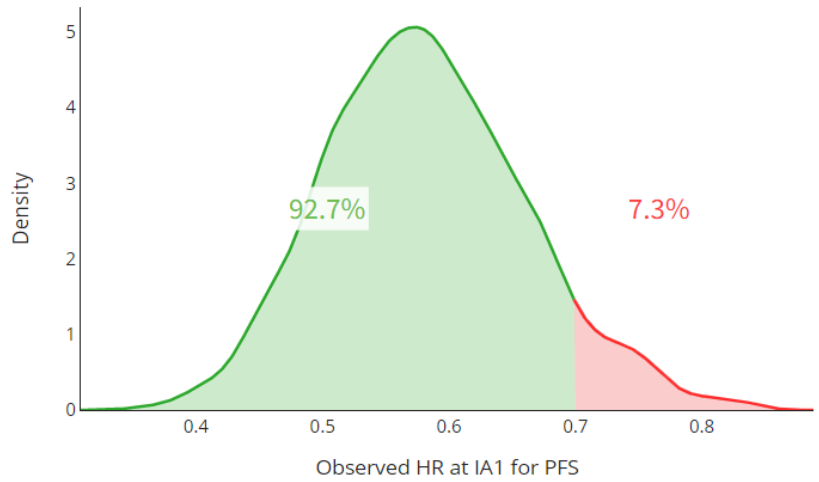
Calculate chance of winning at different looks and different endpoints

Group Sequential | AtLeast80PowerSmallN | Reference Scenario

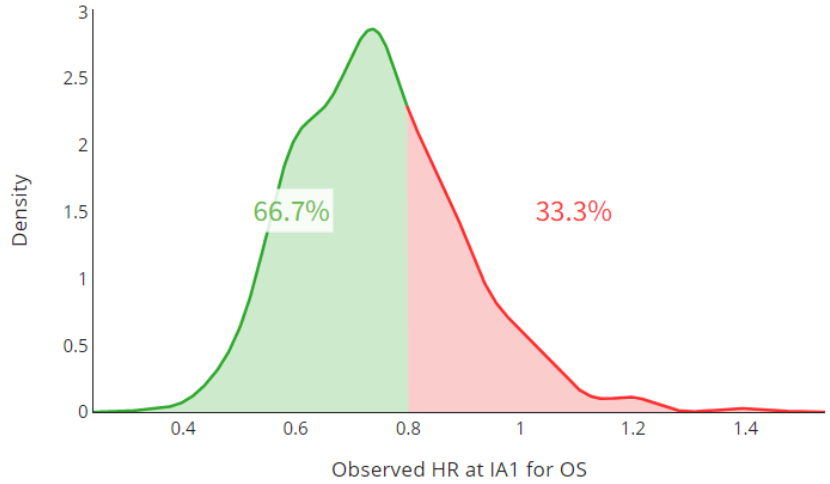
Score	Robustness Score	Weighted Probability of Winning	Likelihood	Synchronize Interims
0.727	0.742	80.6%	0.167	Based on EP1

EP1 (PFS): Superiority 2-Arms, Until End of Study
EP2 (OS): Superiority 2-Arms, Until End of Study

Percentage of Observed HR <= 0.7 at IA1 for PFS



Percentage of Observed HR <= 0.8 at IA1 for OS



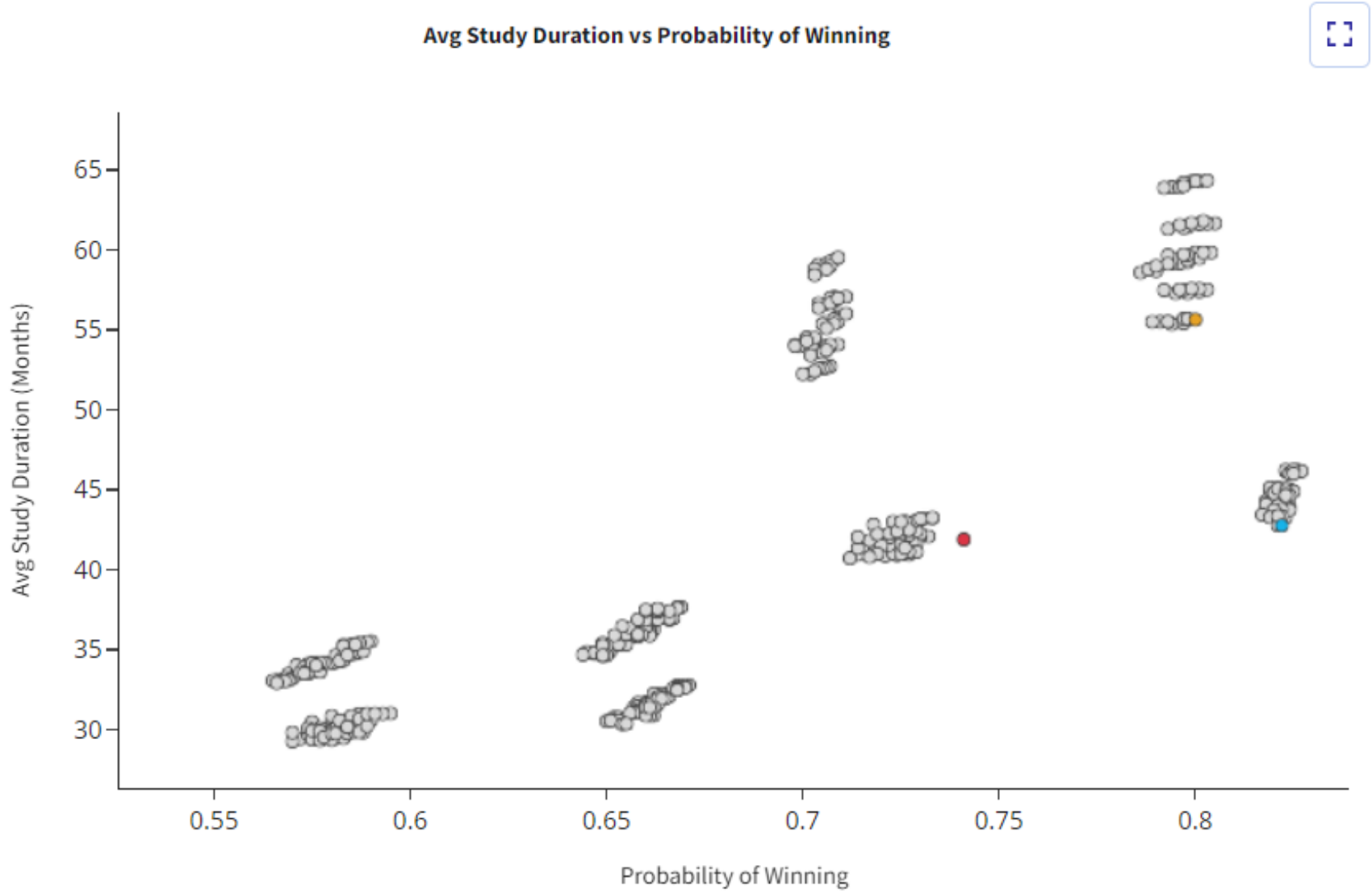
Save Thresholds

Detailed look for each design

Simulation Boundaries and Incremental Boundary Crossing Probabilities

Analysis #	Events for EP1	Events for EP2	EP1 Boundary Crossing		EP2 Boundary Crossing		Decisions		Total Simulations	
			Crossing For		Crossing For		Stopping Trial For			
			Efficacy	Futility	Efficacy	Futility	Efficacy (win)	Futility	Count	%
1	233	105.830	781	17	113	8	88	25	113	11.300
2	310	155.676	168	33	32	3	46	36	82	8.200
3	0	293			501	40	501	40	541	54.100
4	0	390			165	99	165	99	264	26.400
Total			949	50	811	150	800	200	1000	100
%			94.900	5	81.100	15	80	20		

Duration vs Power Plot



Changing Objectives

Reference Response scenario

Design Name	Planned Sample Size	Planned Number of events	Avg. Sample Size	Avg. Events	Power	Avg. Study Duration (Months)	Marginal power (PFS)	Marginal Power (OS)	Alpha Spending Function	Beta Spending Function	Interim Analyses (*: Determined)
Reference Design	504	PFS: 278 OS: 328	504	PFS: 275 OS: 252	74.4%	40	89.9%	74.8%	PFS: Gamma (-4) OS: Gamma (-4)	None	PFS: 70% OS: (28, 40, 75)%
Power Optimized Design	504	PFS: 310 OS: 390	504	PFS: 305 OS: 304	83.8%	52	94.5%	83.9%	PFS: Gamma (-3) OS: Gamma (-4)	None	PFS: 75% OS: (27, 38, 60)%
Sample Size Optimized Design	450	PFS: 278 OS: 390	450	PFS: 273 OS: 288	80.8%	57	92%	80.9%	PFS: Gamma (-3) OS: Gamma (-3)	PFS: Gamma (-4) OS: Gamma (-40)	PFS: 60% OS: (18, 34, 75)%
Duration Optimized Design	550	PFS: 310 OS: 390	550	PFS: 302 OS: 282	80.9%	43	94.7%	81.3%	PFS: Gamma (-4) OS: Gamma (-2)	PFS: Gamma (-4) OS: Gamma (-4)	PFS: 75% OS: (26, 37, 75)%
Balanced Design	450	PFS: 310 OS: 390	450	PFS: 303 OS: 273	79.7%	54	93.6%	80.1%	PFS: Gamma (-3) OS: Gamma (-2)	PFS: Gamma (-4) OS: Gamma (-4)	PFS: 60% OS: (21, 40, 75)%

Thank you

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Appendix

Items to Note

- Alpha-spending Functions: O'Brien-Fleming (OF) & Gamma
  - Gamma= -4 approximates OF
  - Gamma= -1 approximates Pocock
- Target Value needs to be specified for futility interim analyses
  - It's the value of the Alternative Hypothesis that is intended to be rejected in favor of the Null Hypothesis
- The Pareto Set of simulated designs is identified by Solara
  - no individual score criterion (e.g., power, sample size, and duration) can be better off without making at least one other criterion worse off or without any loss thereof.

Target Value of HR for Futility IA

- In order to compute the futility boundary using the beta-spending function we have to solve the equation below:

Keeping this value of η and the previously obtained efficacy boundary values $\{u_1, u_2, \ldots u_K\}$ fixed, compute the futility boundary $\{l_1, l_2, \ldots l_K\}$ as follows:

$$P_\eta(W(t_1 \leq l_1) = \beta(t_1) \qquad \text{(B.68)}$$

This means we need to know how much type-2 error to spend. However, we never specify power in Solara nor the alternative hypothesis (that give us eta), so how do we do this?
We know what the number of events is and that determines max information under proportional hazard. We could get η1 if only we knew delta_1, the target HR: $I_{\max} = \left[\frac{\eta_1}{\delta_1 - \delta_0}\right]^2$

Once we solve for η we can build the boundary, because we also know what the power is for Dmax events when trying to detect a difference of delta_1.
The target value of HR for futility is delta_1