Simulation-based optimization of adaptive designs using a generalized version of assurance

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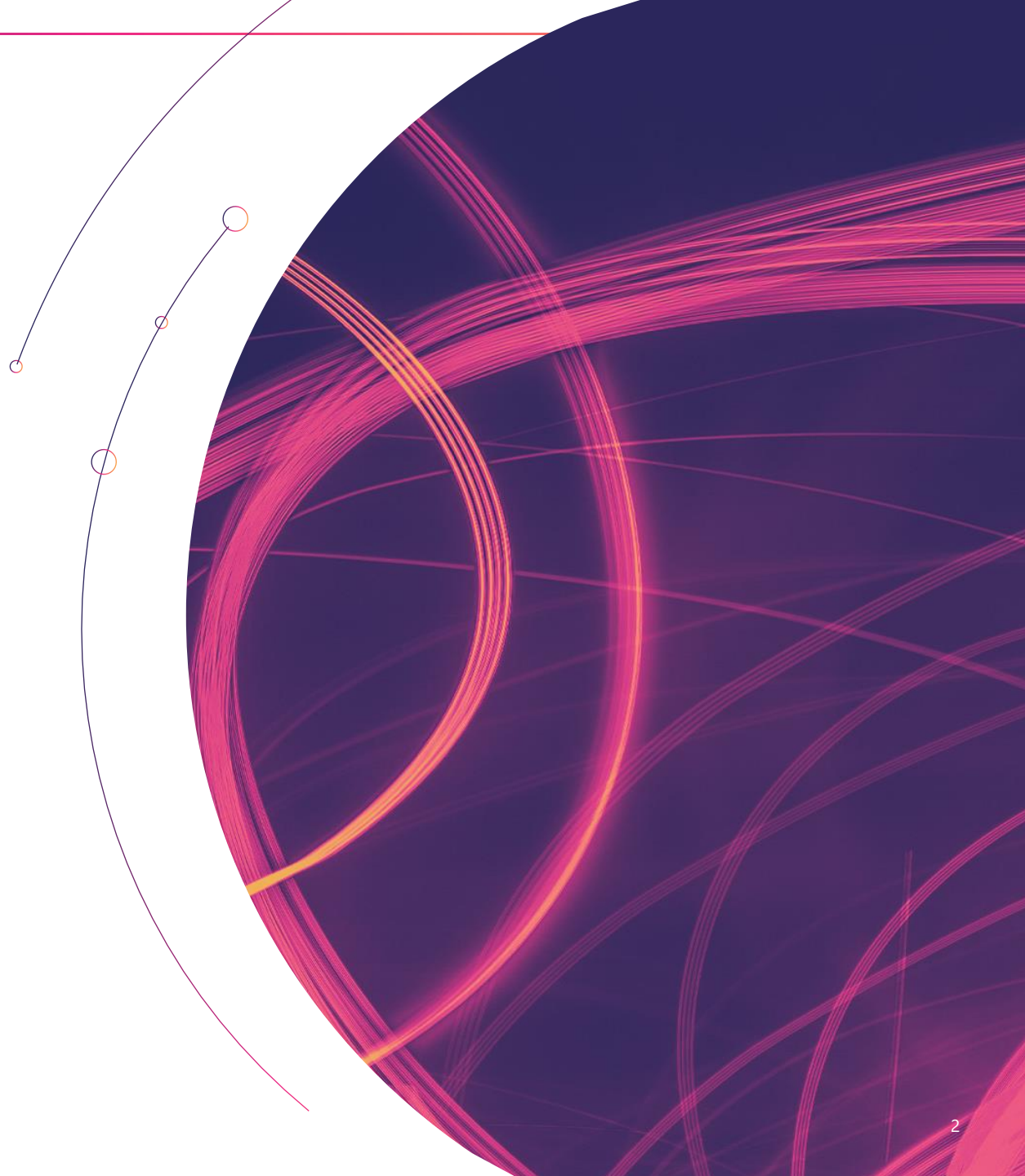
Introducing the problem

Assurance and more…

A case study

Q&A



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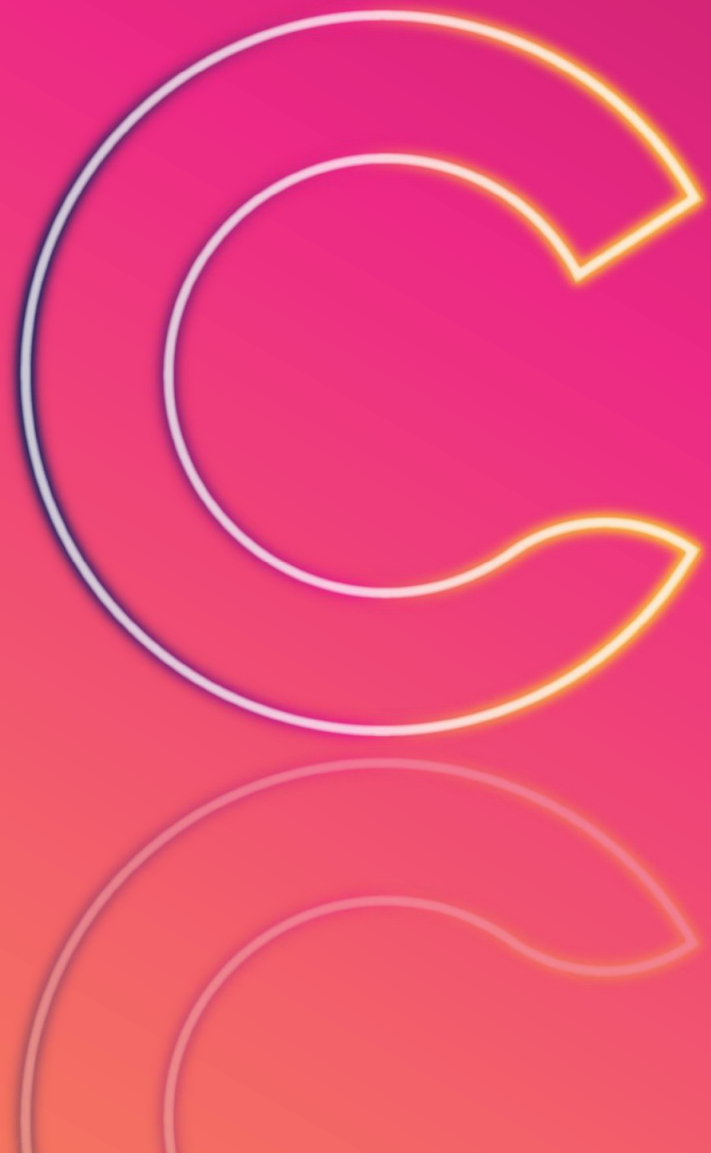
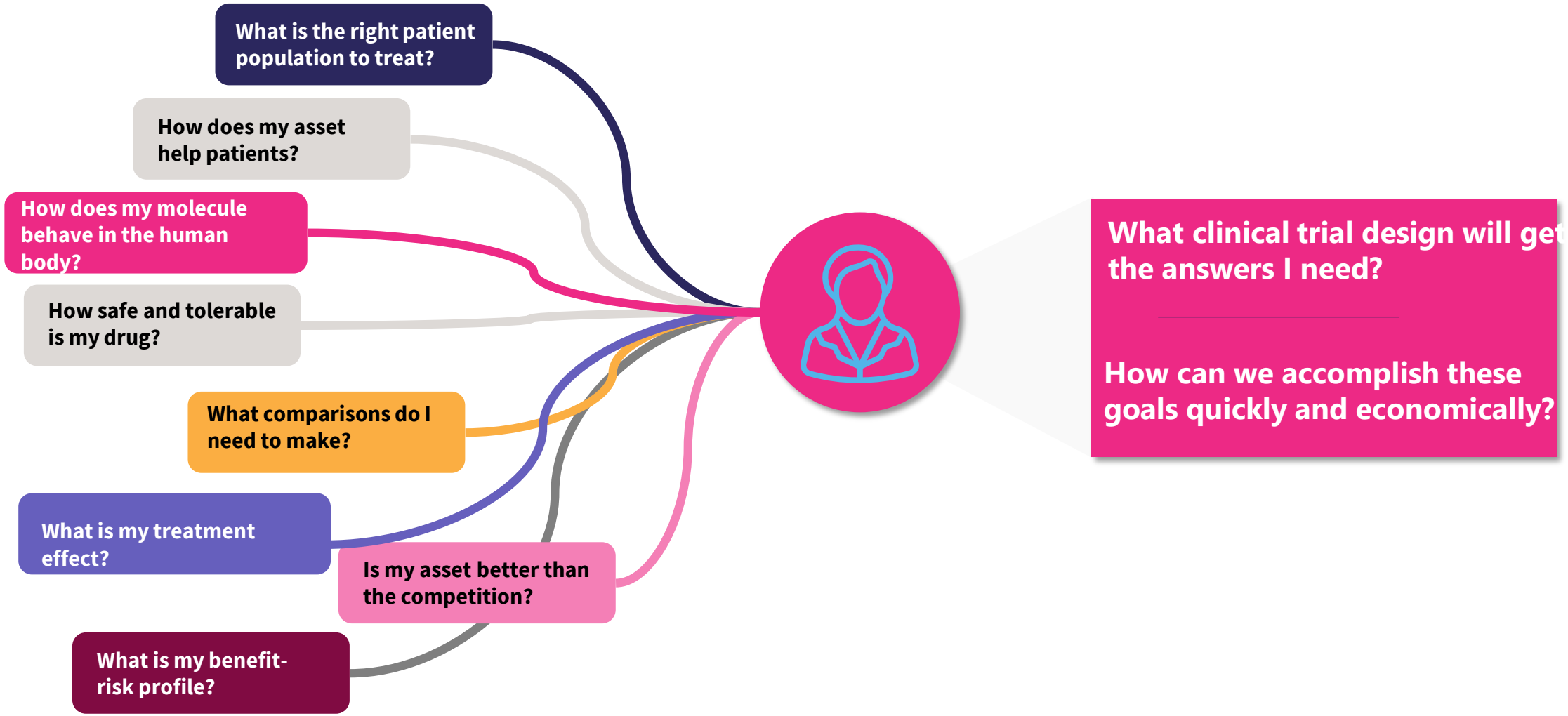
Introducing the problem



How do I plan the right clinical trial?



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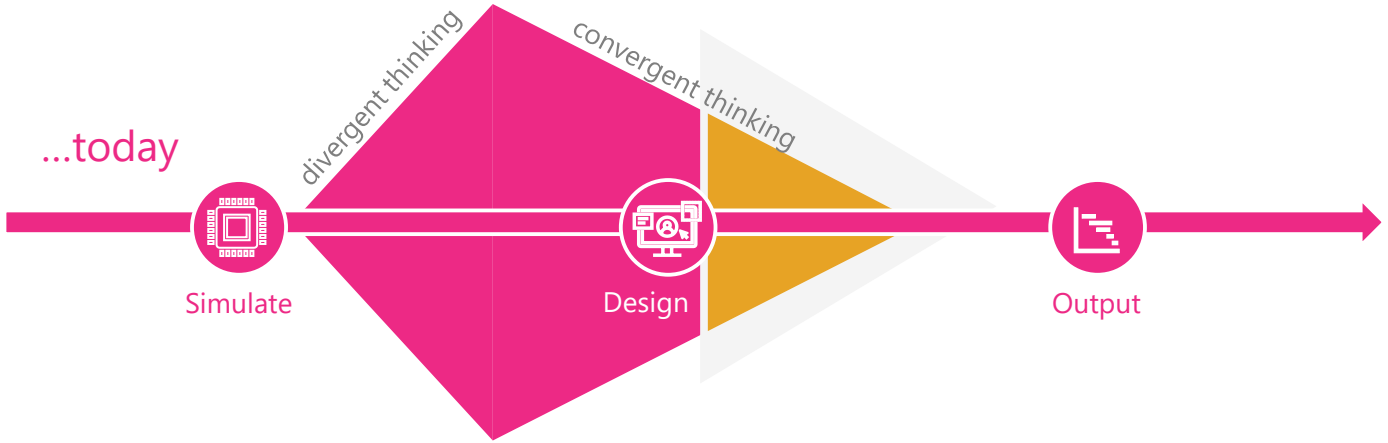
Trial Design Evolution

Challenges

- Design possibilities often limited from the beginning
- Time and resource constraints restrict number of designs and scenarios that can be considered
- Binary study-by-study decision of what tool to use



Benefit

- Optimal designs modeled against business strategy
- Cross-functional collaboration on design selection
- Accelerate speed to market

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What is assurance?

Hypothesis Test

$$H_0: \delta = 0 \; vs \; H_A: \delta \neq 0$$

Where the parameter value δ is the treatment effect

Power

$$P(Reject\ H_0 | \delta = \delta_A)$$

Conditional probability of rejecting the null hypothesis) given an assumed parameter value $\delta = \delta_A$.

By setting power to some desired probability, we can solve for the sample size that will satisfy the requirement.

Assurance (Expected Power)

$$P(Reject\ H_0)$$

$$= \int_{\delta} P(Reject\ H_0|\delta) f(\delta) d\delta$$

Unconditional probability of rejecting the null hypothesis given an assumed distribution (prior) for the parameter value δ

Assurance (more generally)

$$P('Successful\ trial') = \int_{\delta} P('Successful\ trial'|\delta) f(\delta) d\delta$$

Unconditional probability of a 'successful trial' given an assumed distribution (prior) for the parameter value δ

Clinical Assurance

$$P\left(Reject\ H_0\ and\ \widehat{\delta} \geq \Delta\right)$$

$$= \int_{\delta} P\left(Reject\ H_0\ and\ \widehat{\delta} \geq \Delta \middle| \delta\right) P(\delta) d\delta$$

Unconditional probability of rejecting the null hypothesis and achieving a value **Δ** or greater of the treatment effect given an assumed distribution (prior) for the parameter value δ

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Illustrative Example – A simulation-based approach

Illustrative Use Case

Study Description

Phase III multicenter, randomized, placebo-controlled, parallel-arm clinical trial to evaluate the efficacy of Treatment versus Control in an acute Myeloid Leukemia study

Endpoint: Overall Survival (OS)
Design assumptions:

- Control median OS: 8 months
- Treatment effect: HR = 0.7
- One-sided alpha: 2.5%
- Power: 90%
- Enrollment rate: 20 patients/month

Sample Size: ~450, Events: ~330

Test Parameters	
Design ID	fixed0.7-20subjs
Design Type	Superiority
Number of Looks	1
Test Type	1-Sided
Specified α	0.025
Power	0.90053
Model Parameters	
HR = λ_t/λ_c	
Under H0	1
Under H1	0.7
Med. Surv. Time Control (m_c)	8
Med. Surv. Time Treatment (m_t)	11.429
Var (Log HR)	Null
Allocation Ratio (n_t/n_c)	1
Accrual / Dropouts Parameters	
Accrual Rate	20
Dropout	No

Sample Size Information

Sample Size (n)	451
Treatment (n_t)	226
Control (n_c)	225
Events (s)	331
Treatment (s_t)	153
Control (s_c)	178
Information (I)	82.75

Accrual and Study Duration

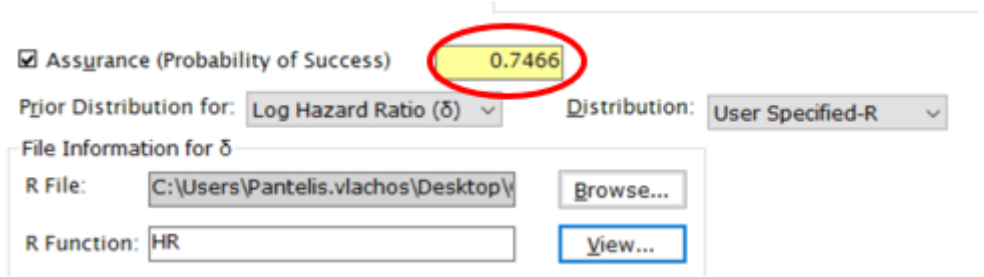
Accrual Duration	22.55
Max. Study Duration	31.145

Adding uncertainly in Treatment effect

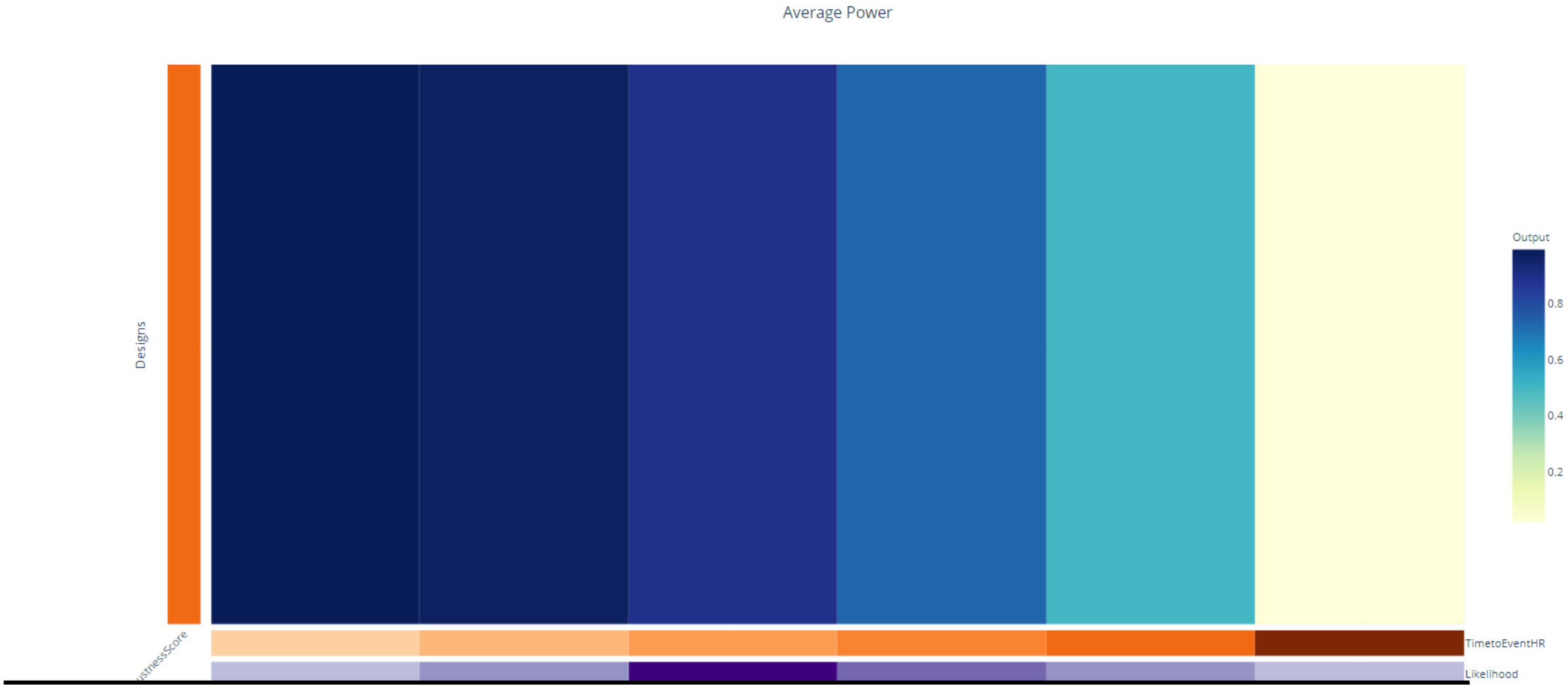
HR	Vague Prior	Clinical Prior
0.65	20%	27%
0.70	20%	37%
0.75	20%	23%
0.80	20%	10%
0.85	20%	3%

Assurance:

$$P(Reject\ H_0) = \sum_{HR} P(Reject\ H_0 | HR = x) P(HR = x)$$



An alternative display…



HR	0.6	0.65	0.7	0.75	0.8	1.0
P(HR)	10%	15%	30%	20%	15%	10%

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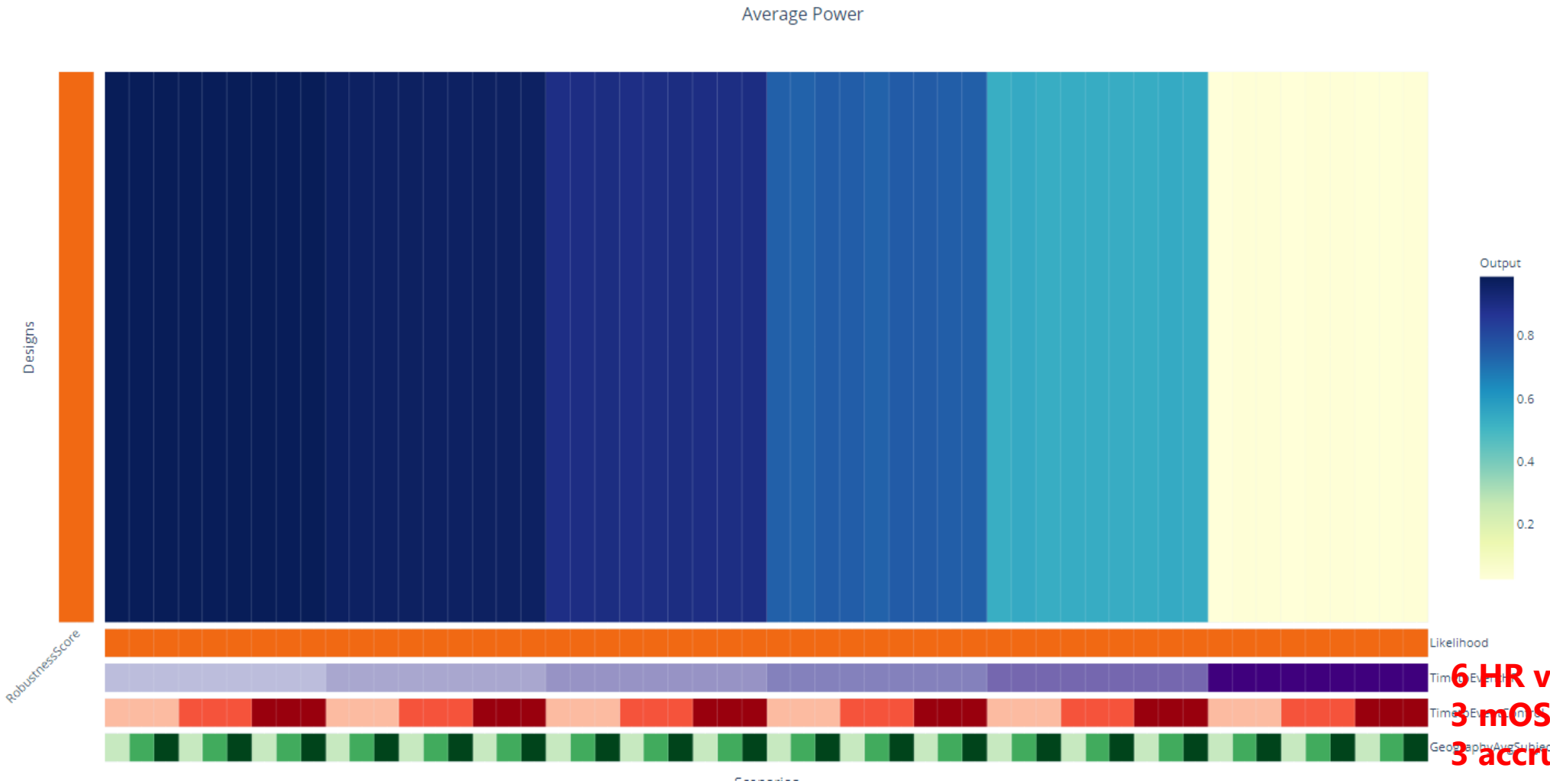
What if we are also uncertain about control mOS and Accrual

PoS = 0.75



6 HR values
3 mOS values
3 accrual rates

54 scenarios

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Expanding from Fixed to Adaptive Designs

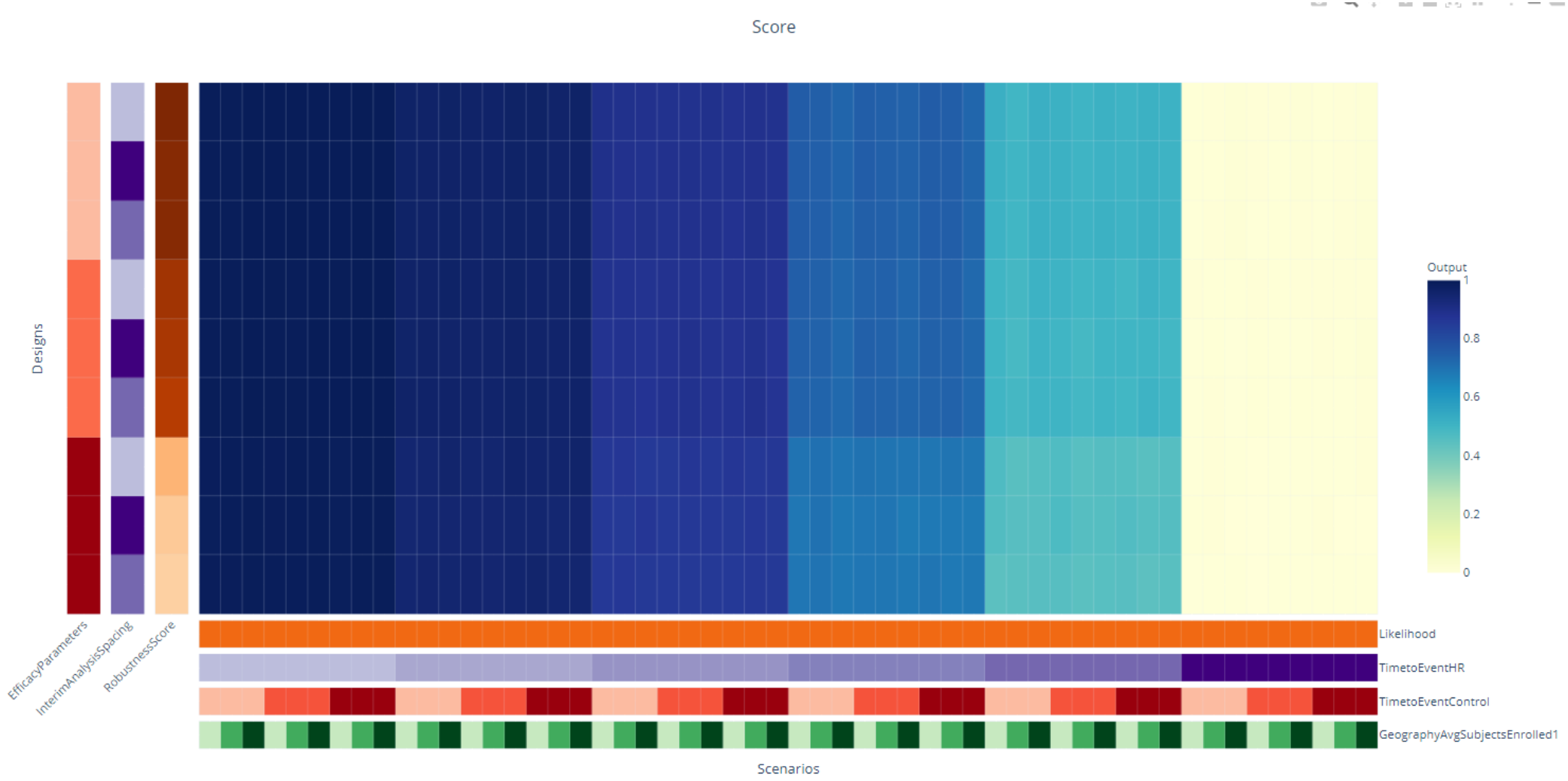
Clinical Study Description and Fixed Design Requirements

Phase III multicenter, randomized, placebo-controlled, parallel-arm clinical trial to evaluate the efficacy of Treatment versus Control in an acute Myeloid Leukemia study

Endpoint: Median OS

- Control median OS: 8 months
- Treatment effect: HR = 0.7
- Enrollment rate: 20 patients/month
- 1 Interim Analysis for Efficacy at either **40%, 50% or 60%** IF
- Alpha-spending according to Gamma rule **(-4,-2,1)**
- Sample Size: 451, Events: 331
- Power: 90%
- One-sided alpha: 2.5%

Same priors…we now have 1 PoS calculation for each possible design



Probability of Success of each design, flat priors

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
68.3%	Probability of Success	68.8%	68.3%	66.3%	68.7%	68.1%	65.9%	68.7%	68.2%	66.0%

Probability of Success of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

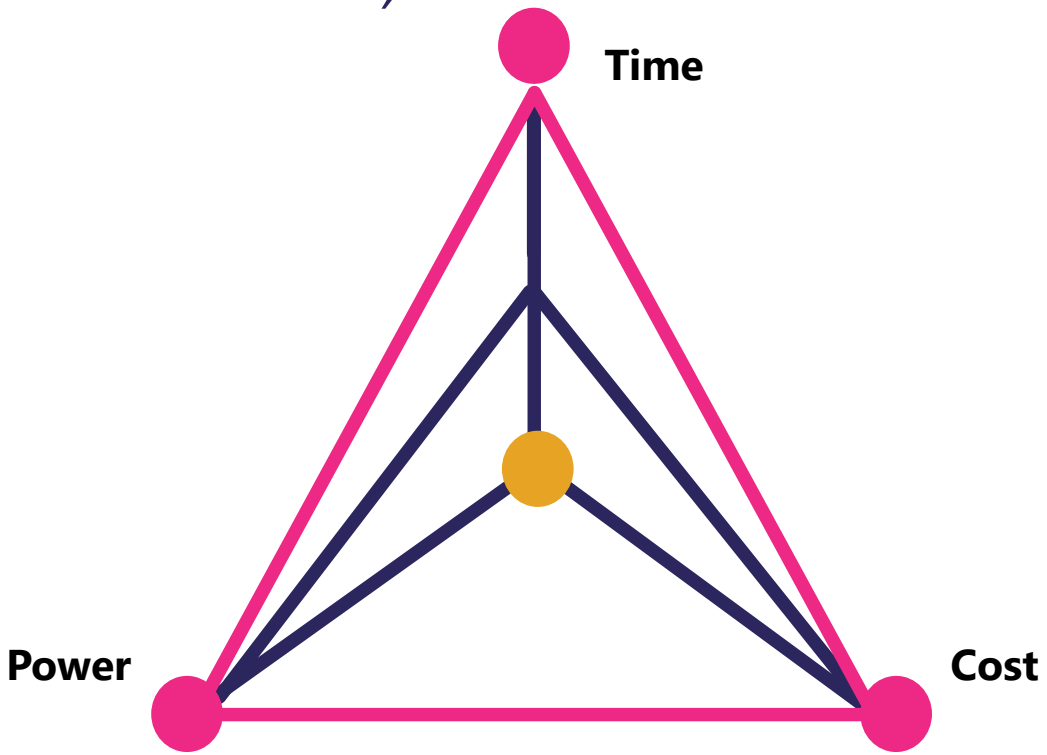
Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
73.5 %	Probability of Success	73.9%	73.4%	71.1%	73.8%	73.2%	70.7%	73.9%	73.2%	70.8%

Recap

- We started with $PoS = \sum_x P(reject\ H_0 | HR = x) P(HR = x)$
- We defined a scenario as $\{HR = x, mOS_C = y, r_{acc} = z\}$ and
- arrived at $\boldsymbol{PoS = \sum_x P(reject\ H_0 | Scenario = s) P(Scenario = s)}$

Performance Scoring to highlight strategic priorities

Product Development Team Chooses Relative Weighting of Cost, Time and Power



Models can be scored on performance criteria that reflect strategic goals

The score is a weighted function of performance criteria

$$w_P\,(P_{max} - Power)\,/\,(P_{max} - P_{min}) + w_T\,(Time - T_{min})\,/\,(T_{max} - T_{min}) + w_C\,(Cost - C_{min})\,/\,(C_{max} - C_{min})$$

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

Performance Score

$$Score\,(Design|\theta) = w_P f(Power) + w_T f(Time) + w_C f(cost)$$

Conditional score for a Design given an assumed scenario θ is a weighted linear combination of Power, Time, and Cost/Sample Size

Robustness

$$Robustness\,(Design) = \int_{\theta} Score(Design|\theta)\,g(\theta)\,d\theta$$

Unconditional score for a Design given an assumed distribution (prior) for the scenario θ

Robustness score of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
Robustness		46.1%	50.6%	56.1%	47.5%	50.8%	54.0%	46.8%	48.6%	49.9%

Score = 40%*Power + 30%*Duration + 30%*Sample Size

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Robustness score of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2	1	-4	-2	1	-4	-2	1
Robustness		46.1%	50.6%	56.1%	47.5%	50.8%	54.0%	46.8%	48.6%	49.9%

Score = 40%*Power + 30%*Duration + 30%*Sample Size

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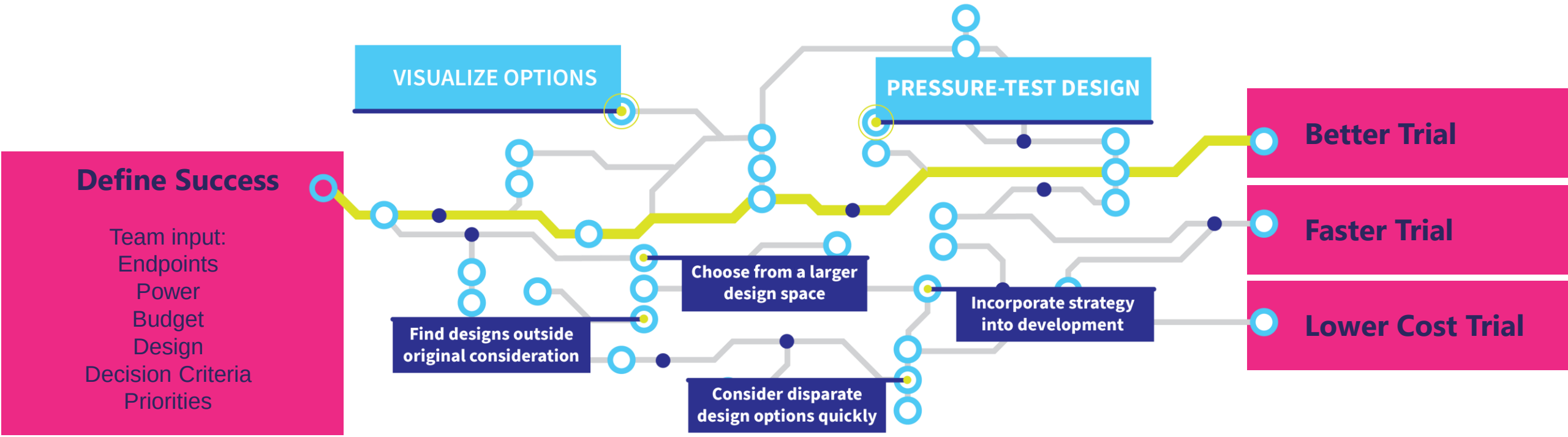
Robustness score of each design, informative prior for HR, flat prior for Ctrl mOS and Accrual

Fixed		GSD								
	IF	40			50			60		
	gamma	-4	-2		-4	-2		-4	-2	
Robustness (unequal weights)		46.1%	50.6%		47.5%	50.8%		46.8%	48.6%	

Score = 40%*Power + 30%*Duration + 30%*Sample Size

Find the Right Path for Your Study

TRIAL DESIGN SIMPLIFIED AND SCALED



ACCELERATE TO VALUE

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A case study in Multiple Myeloma

Multiple Myeloma Ph 3 Study

Reference Design	Inputs
Planned Sample Size	800
Planned Number of Events	227
Allocation Ratio	1:1
Targeted Treatment Effect (HR)	0.65
Control Median Survival Time	20 months
Type-1 error (1-sided)	0.025
Target Power	85%
Number of Interim Analyses	1
Timing of Interim Analysis	70%
Efficacy Stopping Rule	LD-OBF
Futility Stopping Rule	LD-OBF

Primary Outcome:
Progression Free Survival

Optimization Aim:

Maintain adequate power while minimizing time to market

Questions of interest:

- What is an optimal design that accounts for uncertainty on patient recruitment?
- How will treatment effect variations impact the trial?
- What study design would most optimize cost/sample size?

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Design Options
Type 1 error: 1 sided 0.025
Allocation Ratios: 1:1
Number of subjects: 700:800:20
Number of events (if TTE): 130,162, 182, 210, 227, 263
Statistical Design: GSD, GSD with SSR
Number of interim analyses: 1IA
Timing of interim analyses: 65%, 70%, 75%
Efficacy Stopping Rules/Alpha Spending Function: OBF
Futility Stopping Rules/Beta Spending Function: OBF, none
Promising Zone (if applicable): min = 0.3, max = 0.8, 0.9
Target Conditional Power (if applicable): 90%, 99%
Max Number of Subjects/Events (if applicable): 1.2, 1.3, 1.4

Population Scenarios
True underlying control response rates: 20m PFS (vary?)
True underlying treatment effects: 0.60, 0.65, 0.67
Dropout rate: 0

Enrollment Patterns
Enrollment Rates: (Number of periods, starting at time, average enrollment rate) 20pts/mo, 25pts/mo, 30pts/mo

Average Cost per Patient
$100,000

Total number of design options in combination with scenarios (i.e., Models) =
7993 designs x 9 scenarios = 71937 models

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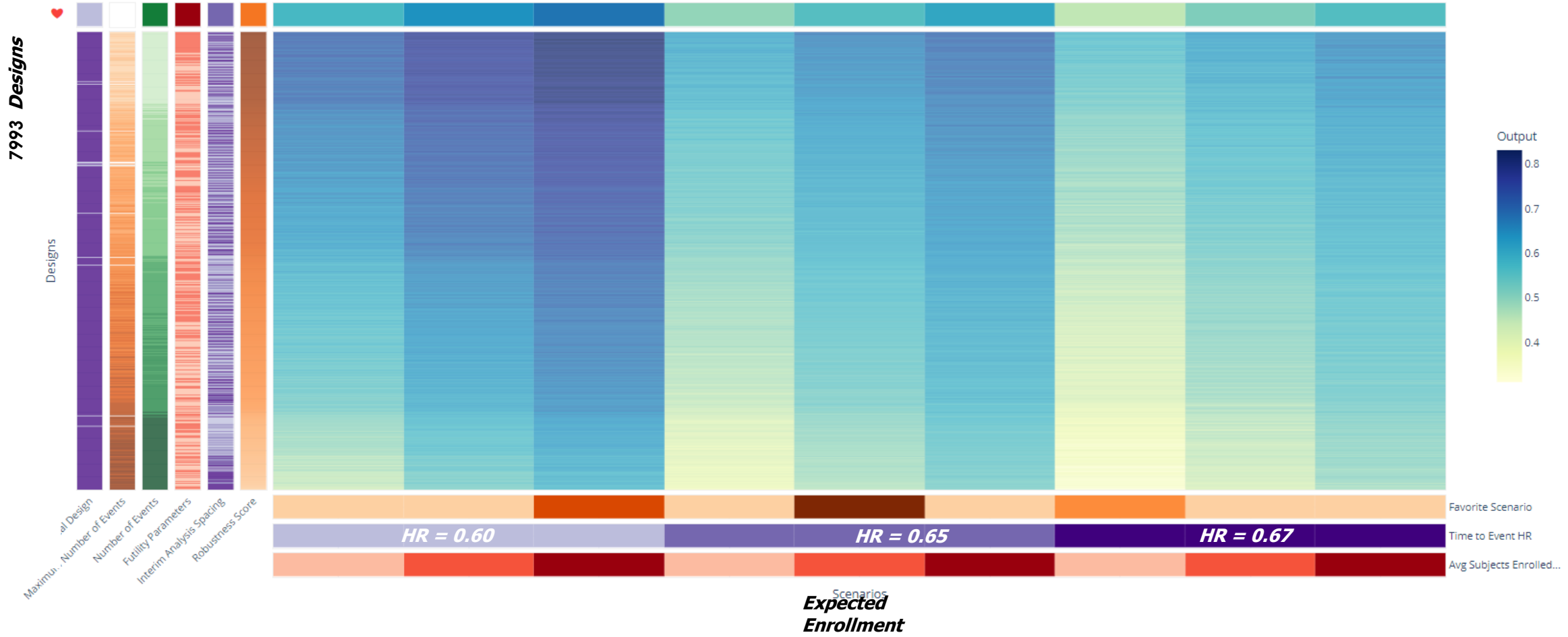
Multiple Myeloma Study

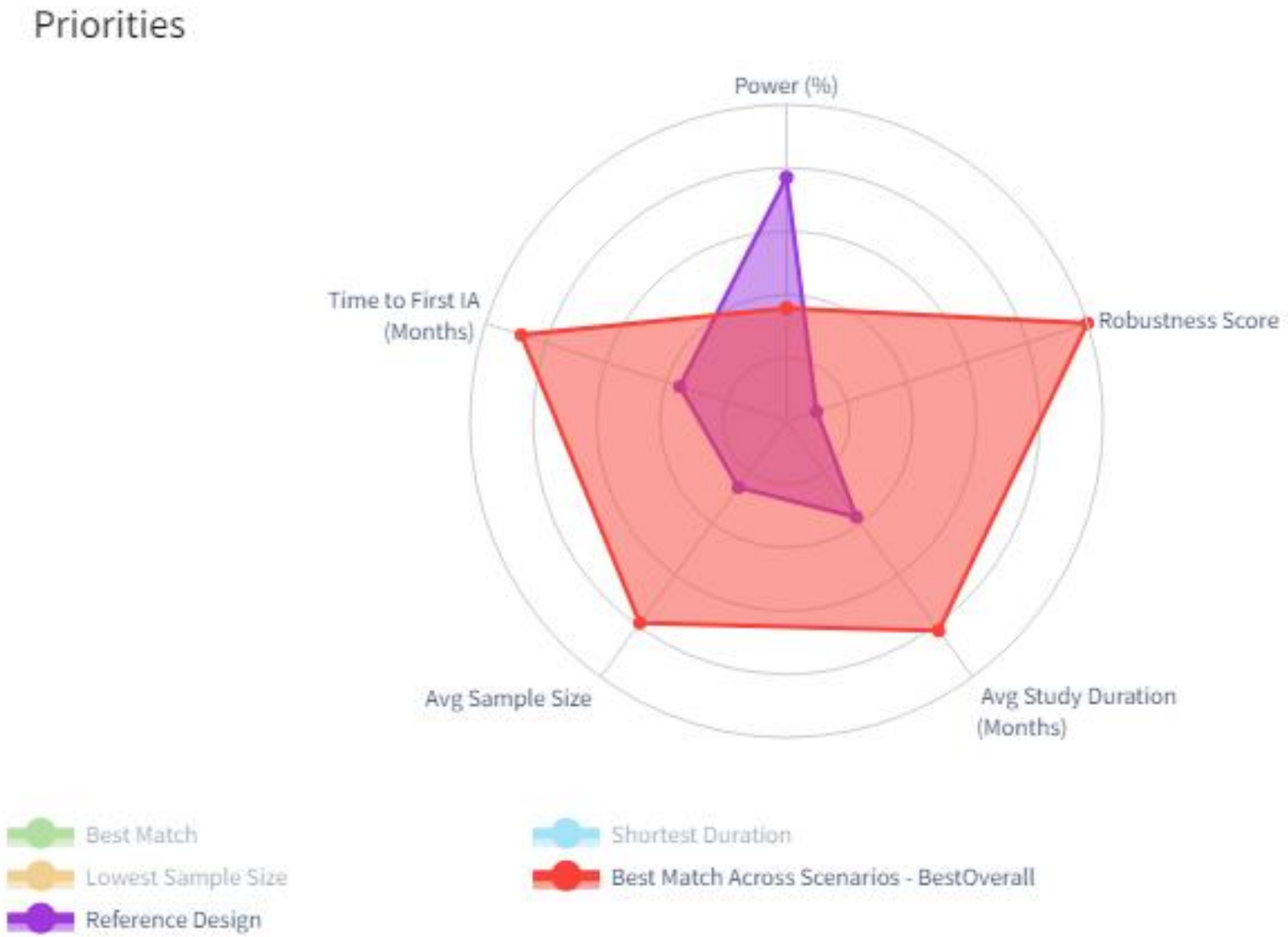
~72 Million Simulated Trials

9 Scenarios

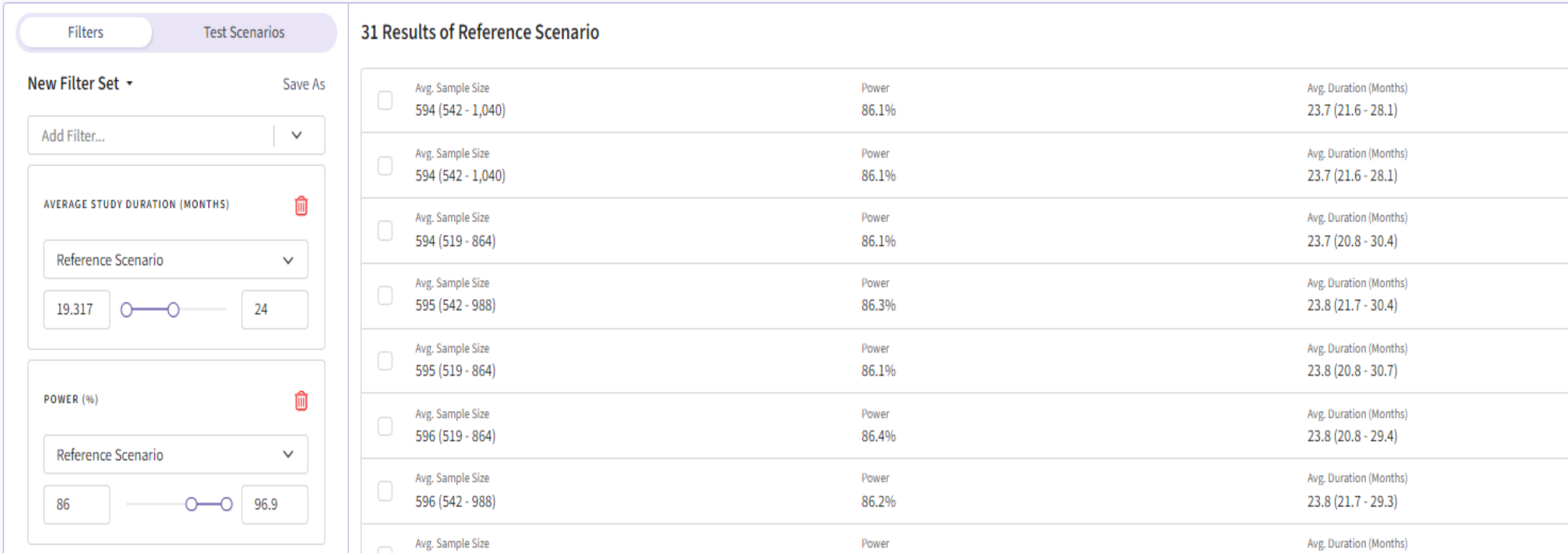


Expected Enrollment

Design Comparison



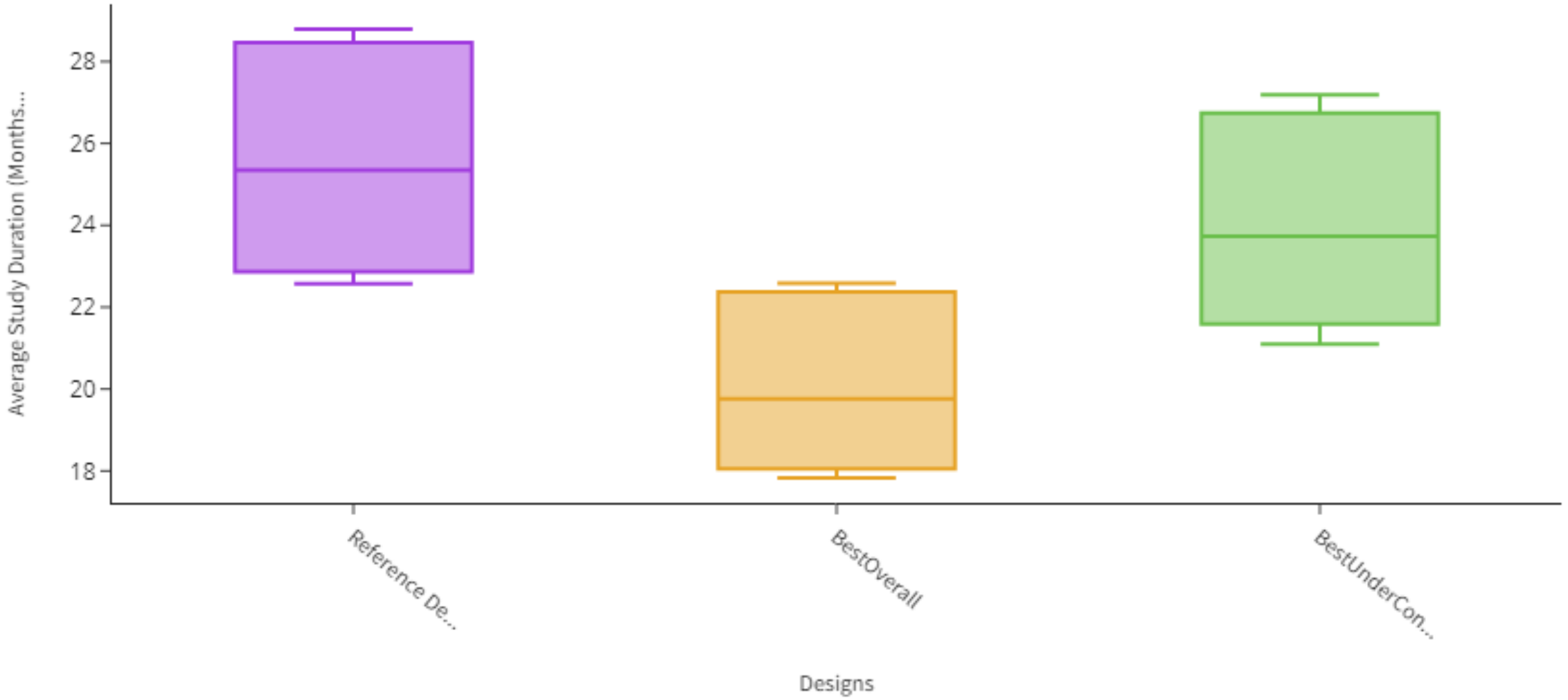
Imposing Constraints



Design Comparison – Reference Scenario

Only Show Differences	BestOverall	BestUnderConstraints	Reference Design
Outputs			
Score	0.684	0.619	0.549
Avg Study Duration	19.734 Months	23.73 Months	25.345 Months
Power	70.8%	86.1%	86.3%
Avg Sample Size	493.601	593.422	633.729
Avg Number of Events	117.403	162.56	182.596
Avg Accrual Duration	19.694 Months	23.69 Months	25.304 Months
Observed HR	0.65	0.64	0.65
Avg Follow Up Time	8.226 Months	9.58 Months	10.09 Months
Power Promising	0.753	0.856	NA

Design Comparison – All Scenarios



Multiple Myeloma Ph 3 Study – Best design

Design Characteristics	Reference	Optimal
Planned Sample Size	800	**760**
Planned Number of Events	227	**182**
Average Events	183	158
Average Sample Size	636	582
Average Duration	25 mo	**23 mo**
Average Power	**88%**	86%
Timing of Interim Analysis	70%	65%
Efficacy Stopping Rule	LD-OBF	LD-OBF
Futility Stopping Rule	LD-OBF	Gamma (-4)
Promising Zone	NA	(0.3,0.8)

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Benefits

Benefits of using assurance in clinical trial design

1. **Risk Management:** quantify the probability of a successful trial outcome given uncertainty about effect size and variance.
2. **Resource Optimization:** by calculating the likelihood of trial success, assurance enables sponsors to optimize resource allocation, potentially saving time and money.
3. **Strategic Decision Making:** assurance can guide strategic decision-making by providing a framework to evaluate the impact of different trial designs and scenarios.
4. **Enhanced Understanding of Trial Metrics:** utilizing assurance in the design phase improves the understanding of key trial metrics and their interrelationships, such as power, effect size, sample size.
5. **Stakeholder Communication:** assurance provides a clear and quantitative measure to communicate the probability of trial success to stakeholders, including investors, regulatory bodies, and ethics committees.

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