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Leveraging Cloud Computing and Advanced Software for Trial Optimization

A Multi-Arm Multi-Stage Proof of Concept Dose Finding Study

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Solara™

First In Class Digital Development for Clinical Trial Design

Your team's input

- Study endpoints, budget, ranges for sample size / enrollment / treatment effect, design options (e.g. fixed or adaptive)
- Team priorities (speed/cost/power)

Proprietary statistical design algorithms

East

- Trusted and validated for over 30 years
- Industry standard platform used by the FDA

Massive cloud compute power

- Parallel processing for near real-time design space generation

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What it does:

- Based on team inputs, calculates study datasets for different designs and scenarios of interest
- Monte Carlo simulations scaled and applied across 1000s of permutations
- Helps teams visualize their options and select the best fit for their needs
- ***Routinely finds better designs than the manual process***

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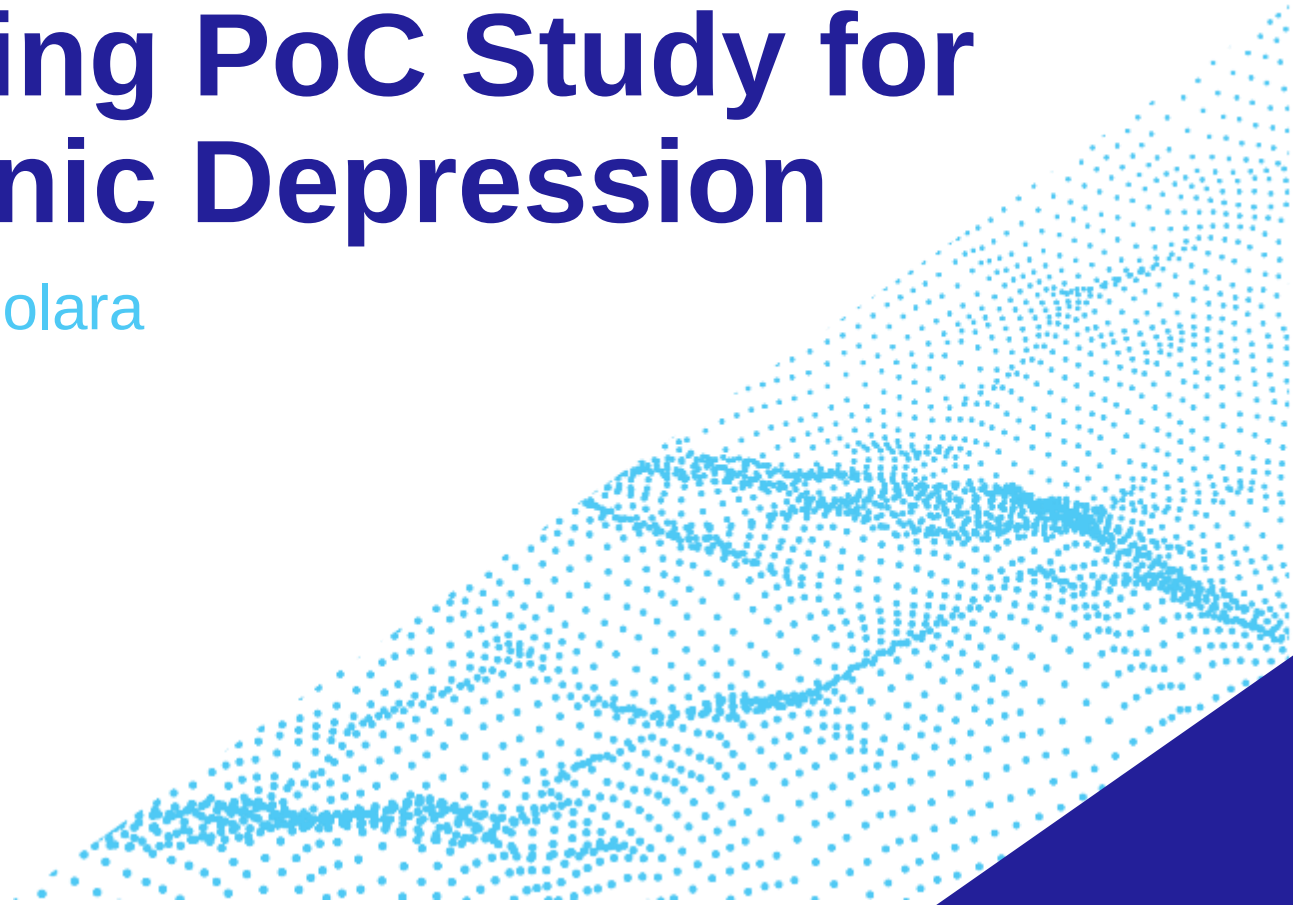
A phase II Dose Finding PoC Study for a Treatment for Chronic Depression

Trial Simulation and Optimization using Solara



Start With the End in Mind
Phase II Solara Simulation Plan

Input [variation]	Patients with Chronic Depression
Number of arms/dose levels/placebo	4 Arms: Low, Medium, and High active doses, and placebo
Primary endpoint name	Change from baseline in Hamilton Depression Rating Scale (HDRS)
Follow-up time	6 weeks
Planned sample size	300 [200, 204, 208,… 356, 360]
1-sided type-1 Error	0.05 [0.05, 0.1]
Target power	85% or above
Winning Condition	Win on at least highest dose
Allocation Ratio	1:1:1:1 [1:1:1:1, 2:1:2:2]
Interim Analysis	1 IA at 50% IF [50%,60%,75%]
PoC and Futility Thresholds	See response assumptions
Dropout rate	5% [5%, 8%, 15%]
Enrollment rate/assumptions	10 patients enrolled/week [6,10,14]
Average cost per patient	$33,000*

*Estimate provided from literature

33 Million Simulated Trials

Scenario Models	33,345
Designs	247
Scenarios	135
Simulations	1000
Seed	689122267
Simulation ID	20596

Hundreds of design variations simulated against dozens of possible execution scenarios in minutes

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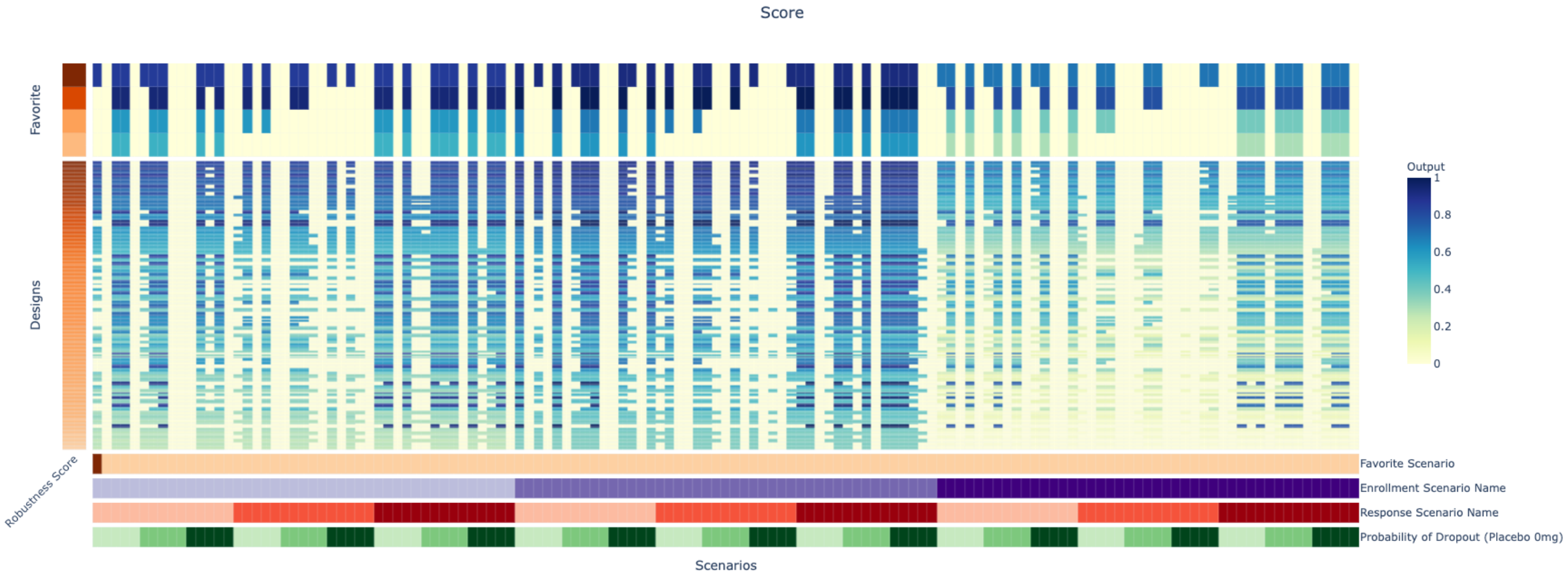
Treatment Effect Uncertainty – Response Assumptions & Scenario Priors

Arm	Scenario 0	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Prior Probability	1%	35%	14%	25%	25%
Placebo	-2	-2	-2	-2	-2
Low Dose	-2	-3.2	-2	-2.3	-2.75
Medium Dose	-2	-3.2	-2.3	-2.75	-3.2
High Dose	-2	-3.2	-2.9	-3.5	-3.5

Prior Probability	Standard Deviation
60%	Expected = 3
20%	Lower = 2.5
20%	Higher = 3.5

Expressed as change from baseline in Hamilton Depression Rating Scale (HDRS) –
- Uncertainty about distribution of treatment effect for each arm leads to multiple TE scenarios simulated
- Uncertainty around observed SD- multiple SD scenarios simulated
- The null (scenario 0) is simulated to ensure type-1 error is controlled

Simulation Results – Solara Heatmap and Score Applied



Designs Selected Based on Solara Score and Prior Weights

Best Match Across Scenarios — Best across sceanrios

Avg. Sample Size	Probability of Winning	Avg. Duration (Weeks)	Avg. Cost
220	91.4%	27.8	6.6M
171 - 220		17 - 27.8	$5.1M - $6.6M

Other Favorites

Reference Design

Avg. Sample Size	Probability of Winning	Avg. Duration (Weeks)	Avg. Cost
300	86%	35.7	9M
211 - 300		21 - 35.7	$6.3M - $9M

Lowest cost shortest duration

Avg. Sample Size	Probability of Winning	Avg. Duration (Weeks)	Avg. Cost
200	87.3%	25.8	6M
160 - 200		15.9 - 25.8	$4.8M - $6M

Min 200 completers

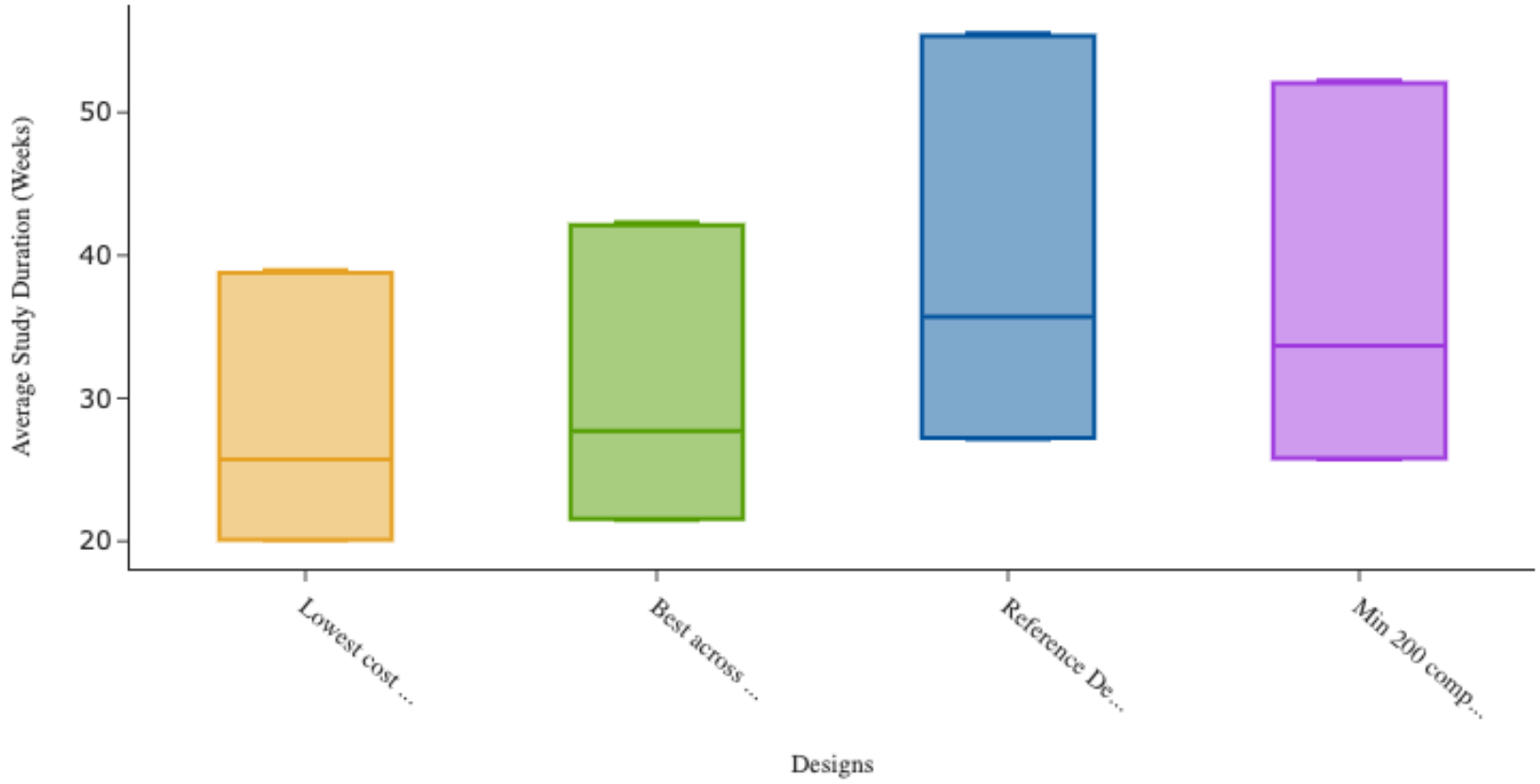
Avg. Sample Size	Probability of Winning	Avg. Duration (Weeks)	Avg. Cost
280	86.9%	33.7	8.4M
271 - 280		27 - 33.7	$8.1M - $8.4M

Solara automatically selects the designs with shortest duration, lowest cost, and the highest-scored design based on selected strategic priorities that are specified by incorporating prior weights.

In this example, compared to the sponsor design, the Solara-optimized design is shorter in duration, employs a significantly smaller sample size and has a higher probability of study success.

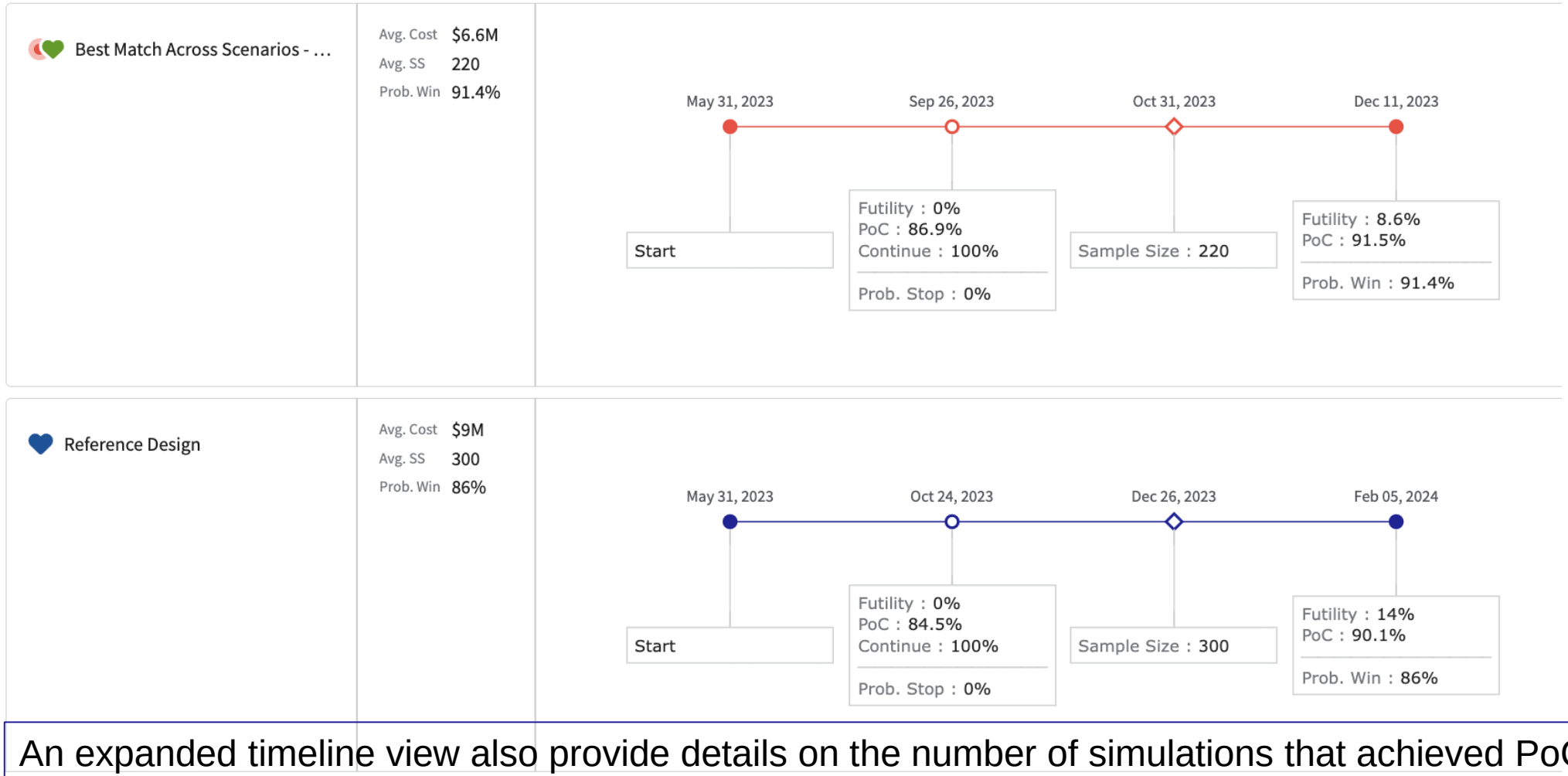
Solara can also accommodate additional constraints, such as including a minimum number of completers or minimum sample size for the most pessimistic scenario. Here, a Solara-optimized trial superior to the reference and with a minimum number of completers was also selected.

Box Plots - Study Duration



Compared to the reference design, all Solara-recommended designs were superior in average study duration, with a smaller range, and lower median.

Expanded Timeline Views



An expanded timeline view also provide details on the number of simulations that achieved PoC or futility at each analysis.

Presenting the poster with full details
Solara demos are available

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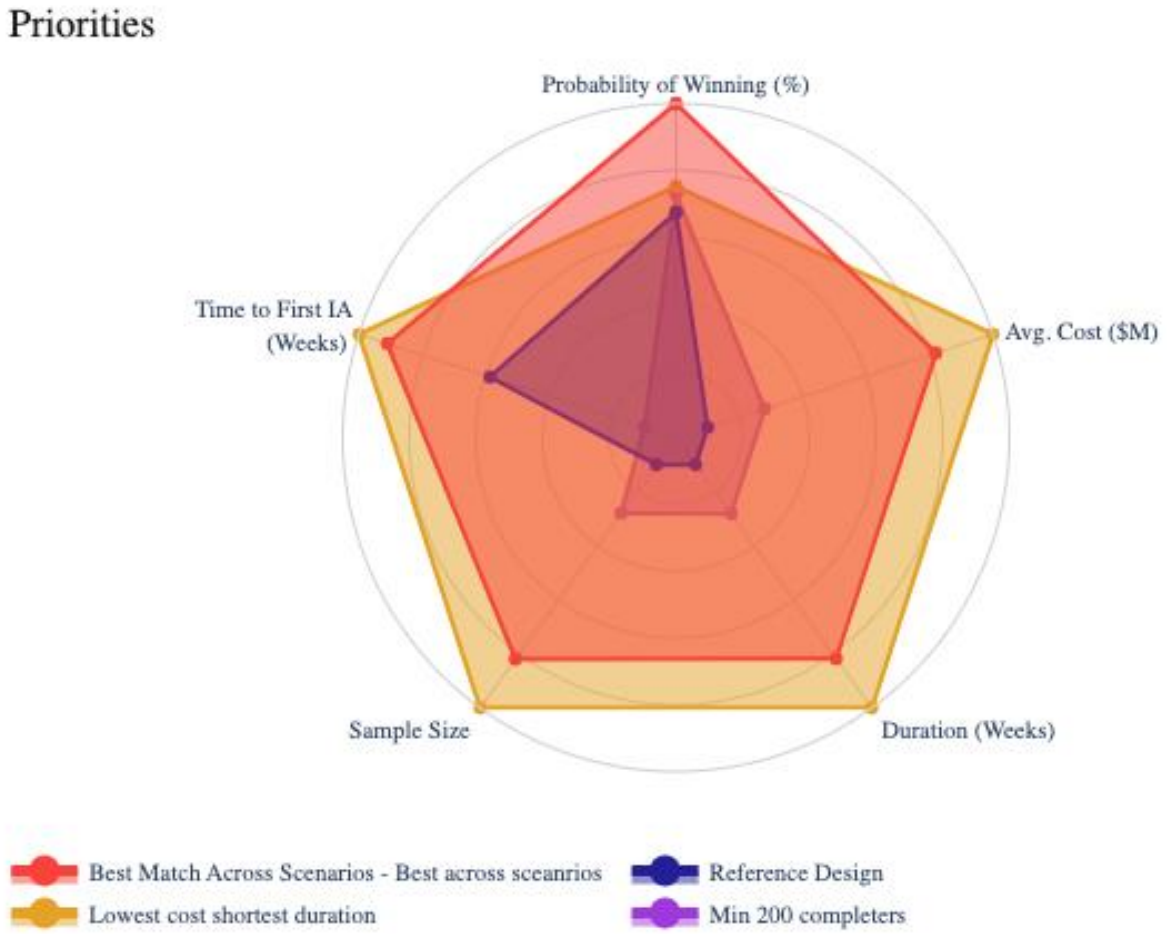
Solara Design Outputs & Parameters – Scenario 1

	Reference	Solara Best Match	Shortest Duration and Lowest Cost	Min. 200 Completers
Probability of Winning	86%	91.4%	87%	87%
Weighted PoW	69.2%	74.6%	72%	69.3%
Avg. Sample Size	300	220	200	280
Avg. Duration	36 Weeks	28 Weeks	26 Weeks	34 Weeks
Avg. Completers	284	208	189	265
Avg. Cost	$9M	$6.6M	$6M	$8.4M
Study Design Parameters				
1-Sided Type-1 Error	0.1	0.1	0.05	0.05
IA Spacing	1 (50%)	1 (50%)	1 (50%)	1 (75%)
Sample Size	300	220	200	280
Allocation Ratio	1:1:1:1	2:1:2:2	2:1:2:2	2:1:2:2
Proof of Concept	-0.75	-0.75	-0.75	-0.75
Stopping Rule	0	0	0	0

Additional Potential Visuals 2

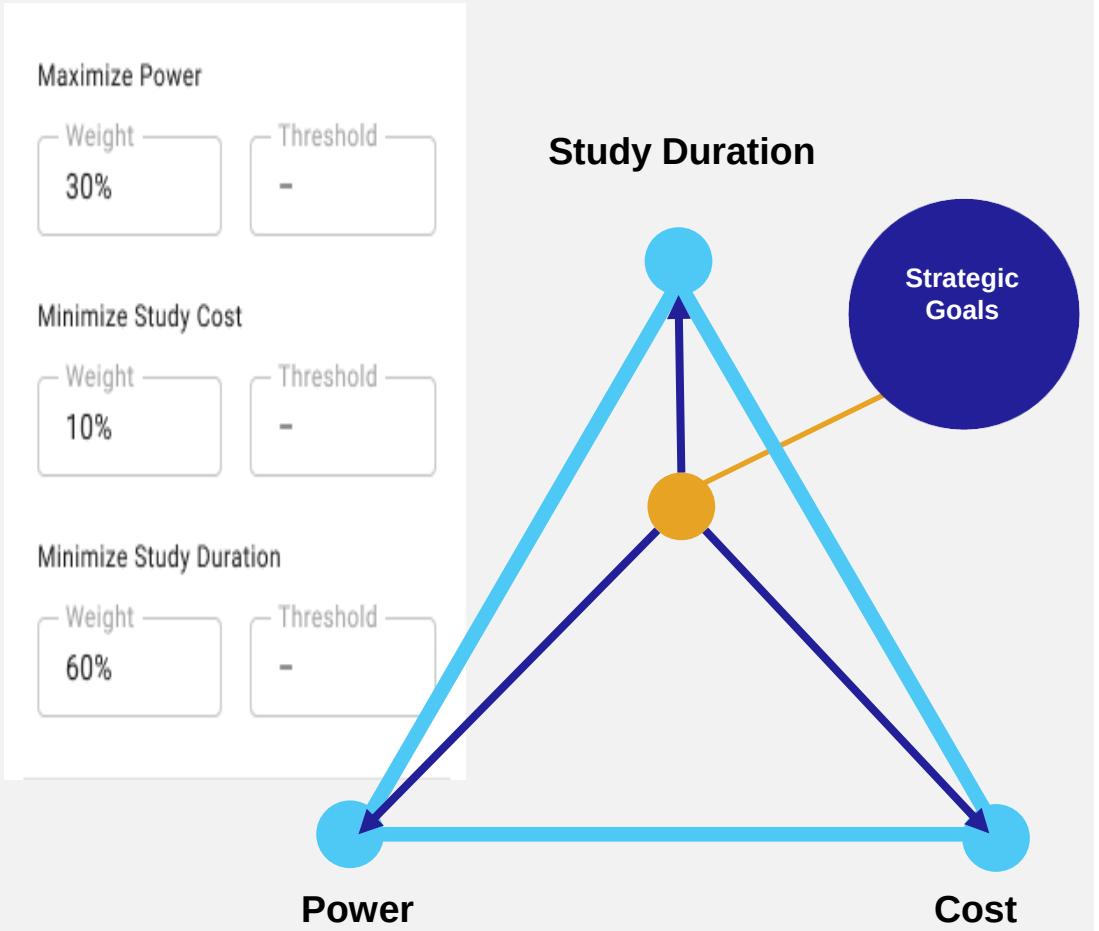
A timeline view allows a side-by-side comparison of the designs

Additional Potential Visuals 4



Solara's best match design is favorable in all five dimensions: Probability of Winning, Average Cost, Average Duration, Average Sample size, and time to first IA.

Weighted scoring system quickly prioritizes and identifies designs that merit further examination



Models can be scored on performance criteria that reflect strategic goals

The score is a weighted function of performance criteria

$$w_{\mathcal{P}}\,(\mathcal{P}_{max} - \mathcal{P}ower)\,/\,(\mathcal{P}_{max} - \mathcal{P}_{min}) + w_{\mathcal{T}}\,(\mathcal{T}ime - \mathcal{T}_{min})\,/\,(\mathcal{T}_{max} - \mathcal{T}_{min}) + w_{C}\,(Cost - C_{min})\,/\,(C_{max} - C_{min})$$

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

Multi-Arm Multi Stage (MAMS) Designs

Multi-arm multi stage designs are useful in several cases:

- MAMS designs can be used in Phase II trials when the goal is to identify the best dose, or doses, to move forward in clinical development
  - The multi-arm element allows evaluation of multiple doses against placebo or Standard of care
  - The multi-stage element allows for proof-of-concept gatekeeping by introducing the opportunity to terminate trials early for efficacy or futility based on interim results

- MAMS designs can also be deployed as inferentially seamless Phase II/III designs where a proof-of-concept study is combined with a confirmatory phase with either one or more interim analyses. This design type offers several savings:
  - Shorter overall duration compared to two separate trials, relying on a single recruitment mechanism
  - Smaller average sample size as data from patients enrolled in the first phase is also included in the final analysis at the end of the second phase of the study

Phase II Dose Finding Study

In a phase II dose finding study, the aim is to select one or more effective treatment arms compared to placebo or standard of care. There are several crucial areas to consider in this type of design, including:

- **Allocation ratio-** the number of patients assigned to each of the study arms. Many designs rely on a 1:1 allocation ratio, but in many instances, it is beneficial to allocate more patients to higher dose arms to improve the probability of success in those arms.
- **Type-1 error-** in phase II designs, we typically see a higher type-1 error than in confirmatory studies.
- **Choice of Multiplicity Comparison Procedure (MCP)-** There are different approaches to controlling type-1 error when working with multiplicity (in this case, multiple arms).
- **Interim analysis spacing-** the timing of the assessment of proof-of-concept (PoC) or futility is important to ensure an efficient and ethical trial.
- **PoC and futility thresholds-** the boundaries selected to assess efficacy or futility of the treatment are critical to ensuring meaningful trial results.

Phase II Dose Finding – Multiple Comparison Procedures - Fixed Sequence (Step-Down) Tests

Both MCPs employed in Solara for phase II studies are Fixed Sequence Tests. Each tests the highest dose against placebo first, and if significant, tests the next highest dose, and the next etc.

Fixed Sequence Trend Test

This is a contrast-based test that examines each dose level based on pre-specified contrasts using a stepwise approach. Recall that in data-driven stepwise procedures, there is no control over the order of the hypotheses to be tested. However, sometimes based on preference or prior knowledge, the order of tests are fixed. The Trend Test is useful in situation where the response is assumed to be monotonic to the dose.

Fixed Sequence Pairwise Test

This test is also contrast-based, but it involves calling the Fixed Sequence Test repeatedly for each dose in a stepped manner. This test is useful in situation where the response is expected to plateau at a certain dose level, or if only the high dose is expected to separate from placebo.