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Flexibility in Clinical Trial Design using Software in combination with R Code: Incorporating Bayesian Treatment Resistance Assumptions

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Bayesian Biostatistics Conference
Rockville, MD.

October 2024

Who we are

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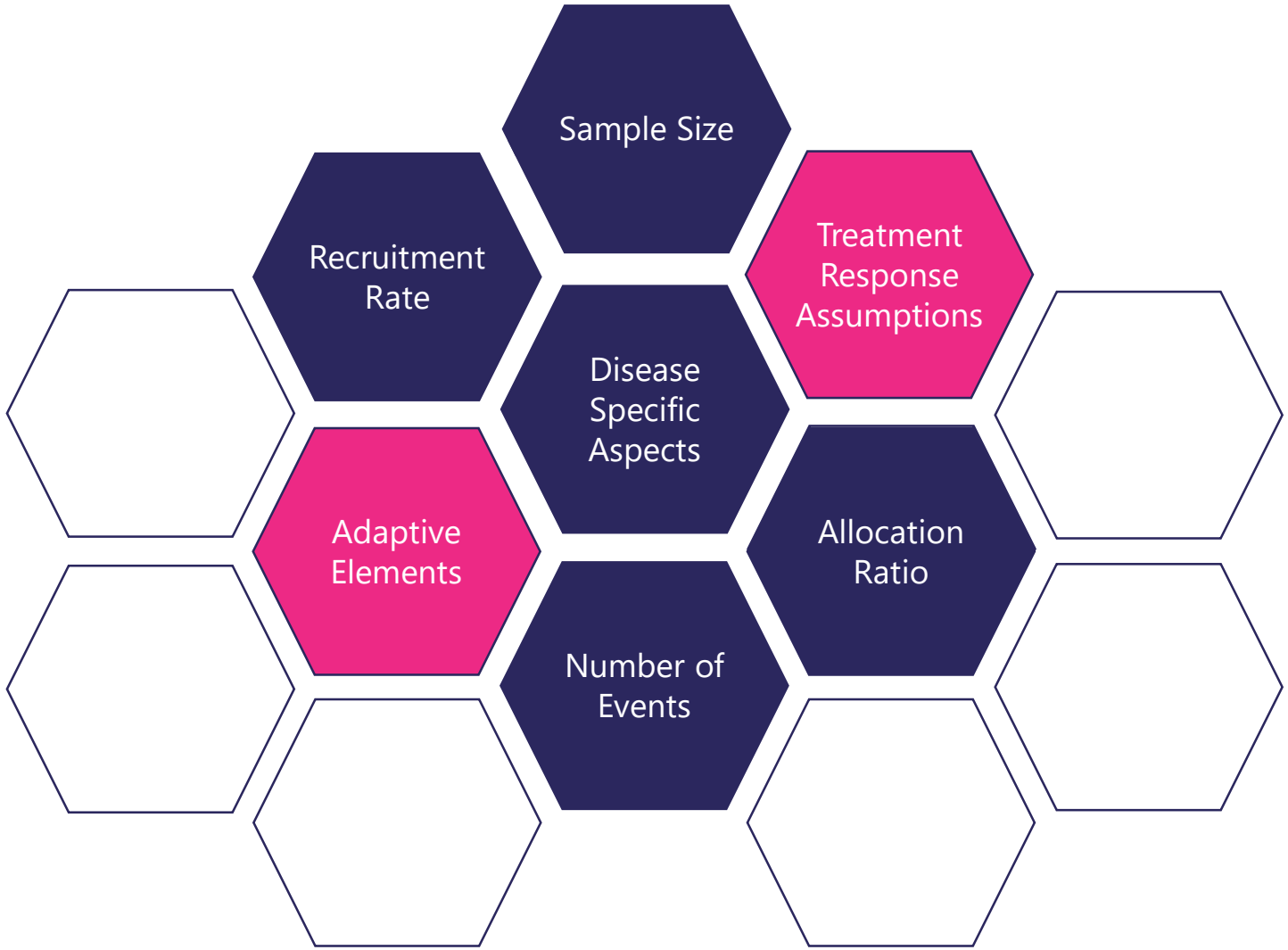
Considerations in Clinical Trial Design



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Simulation-Guided Design

A means to assess trial performance given specific assumptions

- Trial design software
  - Validated design workflows and analysis types
  - Turnkey operation
  - Industry-accepted tools
- Custom coding
  - Allows for flexibility in methods and analysis types
  - Requires coding skills and validation
  - Increased regulatory acceptability

What if assumptions are uncertain?

Trusted capabilities of **traditional software + flexible R** code can offer a more comprehensive assessment than either option alone

A Case Study

Basic Study Design

Parameter	Inputs
Endpoint Type	Binary
Follow-Up Time	12 months
Planned Sample Size	400
One-Sided Type-1 Error	0.025
Control Proportion	0.20
Treatment Proportion	0.45
Enrollment Rate	Poisson Arrival Assumption

Design Variations

Parameter	Inputs
Endpoint Type	Binary
Follow-Up Time	12 months
Planned Sample Size	400
One-Sided Type-1 Error	0.025
Control Proportion	0.20
Treatment Proportion	0.45
Enrollment Rate	Poisson Arrival Assumption

Parameter	Inputs
Treatment Resistance Assumptions	**0%**, 20%, 40%
Treatment Difference	0.1, 0.15, 0.2, **0.25**, 0.3
Planned Sample Size	**400**:500:5

Methods Two-Step

1. Analyzing a frequentist go/no-go decision using a simplified limits of confidence interval design

2. Using posterior probabilities for a Bayesian simulation of a mixture distribution of treatment effect with varying treatment resistance assumptions

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About CyneRgy

With the enablement of R connectivity in its Software, Cytel's Innovation Group has created a dedicated, continuously updating resource library with compatible code examples and templates for edit and use in Cytel Software.

The resource is available on GitHub

Includes code templates and all relevant documentation

An open-source tool to allow variation and additions

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Go/No-Go Decision Using Limit of Confidence Interval

Analyzing a frequentist go/no-go decision rule

In this example of upper and lower confidence boundary designs, if it is likely that the treatment difference is above the **Minimum Acceptable Value (MAV)** then a **Go decision is made**. This is the case if the Lower Limit of the CI, denoted by LL, is greater than the user specified dLowerLimit.

If a Go decision is not made, then if it is unlikely that the treatment difference is above the **Target Value (TV)** a **No-Go decision is made**. This is the case if the Upper Limit of the CI, denoted by UL, is less than user-specified dUpperLimit.

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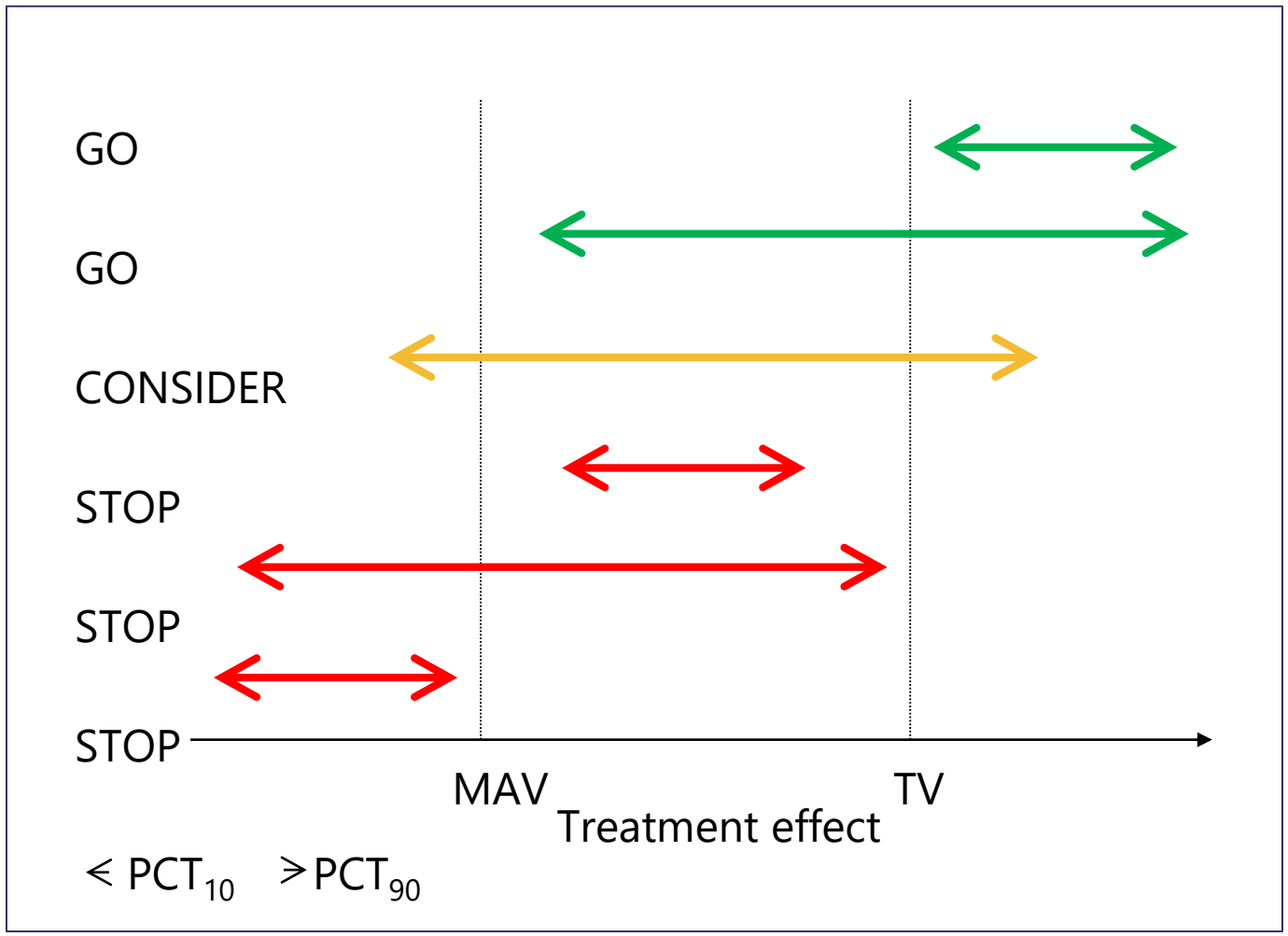
Visualizing the Decision Framework



Go if : PCT_{10} > MAV and PCT_{90} > TV

Consider if: $PCT_{10} \leq MAV$ & $PCT_{90} >$ TV

Stop if : $PCT_{10} \leq$ TV

where PCT_x denotes the x-th percentile of P (Δ)

Go: Lower Confidence Limit (LCL) above MAV

Stop: Upper Confidence Limit (UCL) below TV

If both happen at final analysis, stop rule takes precedence

Mixture Distribution for Patient Simulation

For this study, the patient outcome is binary where a value of 0 represented a treatment failure/**non-response**, and a value of 1 represented **response**.

There is an unknown proportion of patients who are treatment-resistant and will not respond to treatment, and thus, have an outcome of 0. Using historical data, it is estimated that the proportion of non-responders is between 20% and 40%.

An R function is inserted to explore the proportion of patients that are treatment resistant and the impact on expected study power.

Analysis using a frequentist go/no-go decision rule, but sampling patient data using a mixture distribution with a fixed non-responder rate or assuming a prior distribution for the non-responder rate.

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Procedure Details

A binomial distribution is utilized to simulate if the patient is treatment resistant. If the patient is not treatment resistant, then their outcome is simulated from a binomial distribution with the response in East Horizon and sent to R. In the East Horizon Inputs:

1. Prob(0) = 0, Assume that no patients are treatment resistant

2. Prob(0) = 0.2, assumes 20% of patients are treatment resistant

3. Prob(0) = 0.4, assumes 40% of patients are treatment resistant

4. Prob(0) ~ beta (a, b) – depending on what historical data suggests, could be treatment arm-specific

Parameter	Inputs
Treatment Resistance Assumptions	0%, 20%, 40%
Treatment Difference	0.1, 0.15, 0.2, 0.25, 0.3
Planned Sample Size	400:500:5

Results – Original Study Design

No Treatment Resistance						
Treatment Effect	Null	0.1	0.15	0.2 (expected)	0.25	0.3
Power	0%	26%	62%	90%	99%	100%

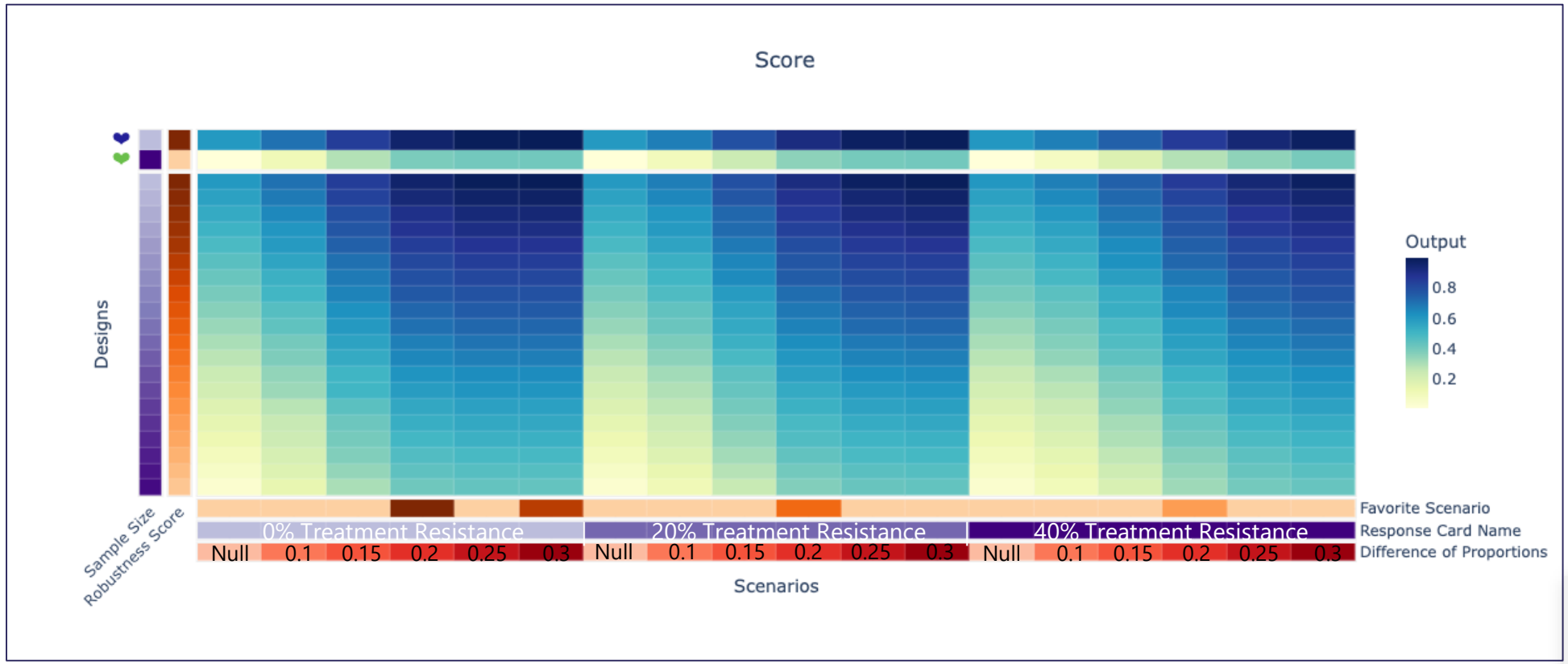
20% Treatment Resistance						
Treatment Effect	Null	0.1	0.15	0.2 (expected)	0.25	0.3
Power	0%	19%	48%	80%	96%	100%

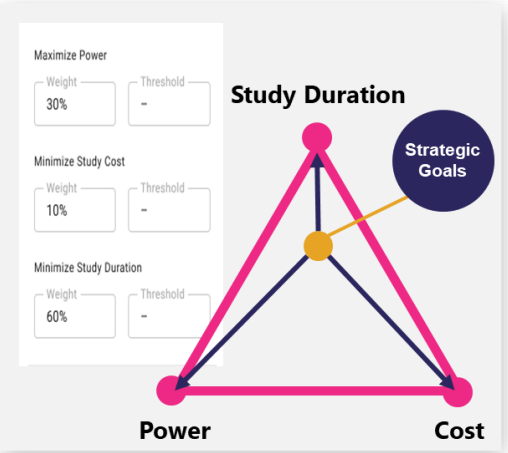
40% Treatment Resistance						
Treatment Effect	Null	0.1	0.15	0.2 (expected)	0.25	0.3
Power	0%	17%	36%	64%	85%	95%

Simulations of the original study design demonstrated that as the proportion of non-responders increased, the observed treatment effects diminished, leading to reduced probability of success.

Designs with a larger sample size showed improved study power.

Heatmap Depicting Simulation Results (Score)





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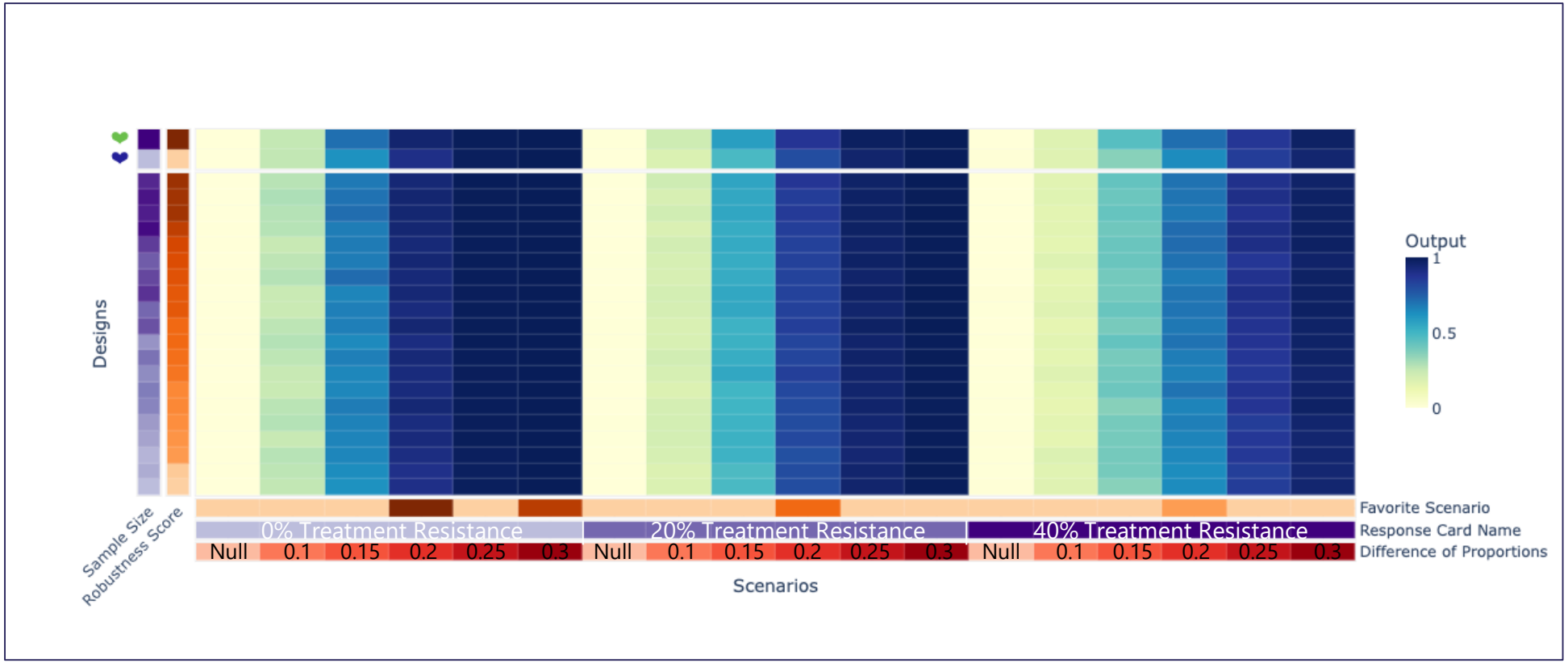
Heatmap Depicting Simulation Results (Power)



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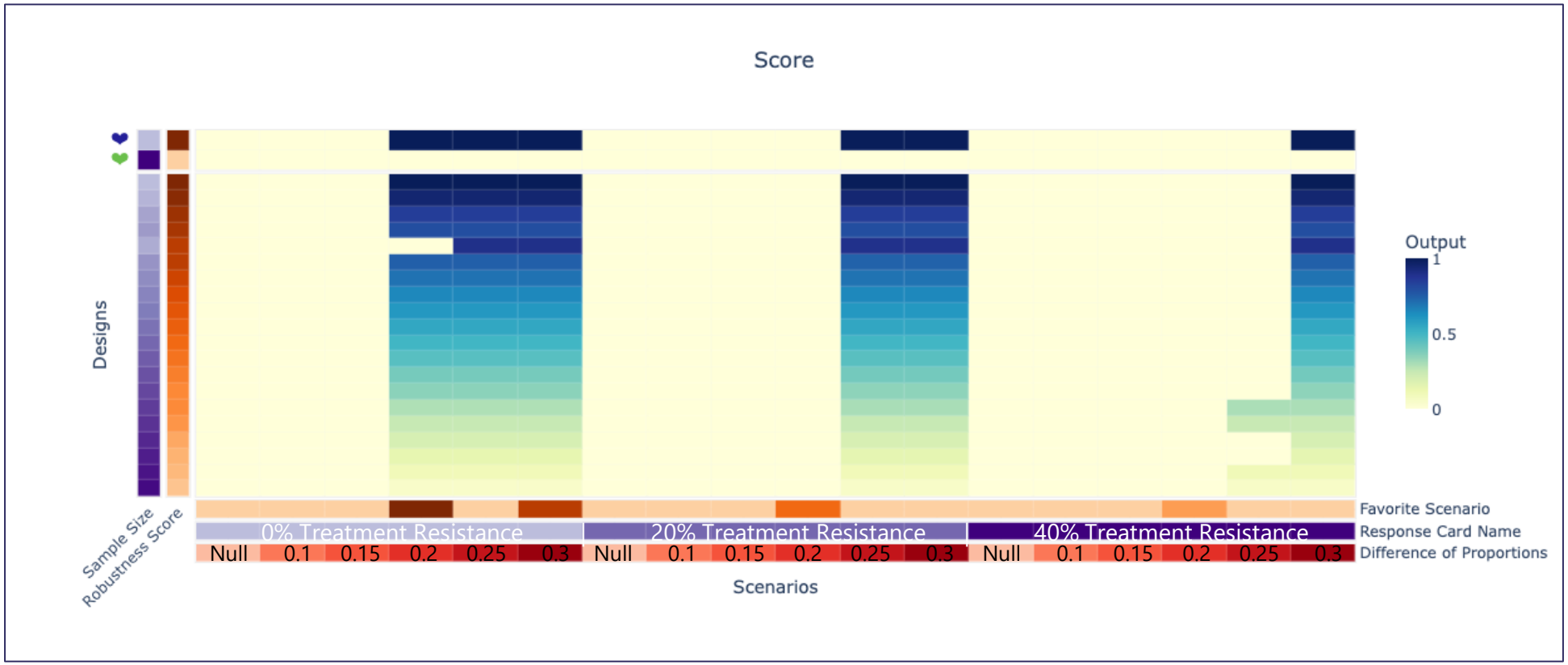
Heatmap Depicting Power Threshold (90%)



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Summary

- Simulation-guided design relies on confident assumptions
- Uncertainty can be mitigated via an iterative process of simulation
- Design software + custom code allow for reliability & flexibility
- Analysis can be extended with either Bayesian or Frequentist approaches

Examples:
Prior distributions for treatment response rate; treatment resistance rates; Bayesian assurance; etc.

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Thank you!

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References

Cynergy Packages Used:

AnalyzeUsingPropLimitsOfCI()
Analyze using a simplified limits of confidence interval design.

SimulatePatientOutcomePercentAtZero()
Simulate patient outcomes from a normal distribution with a percent of patients having an outcome of 0.

- Developed by J. Kyle Wathen, Valeria A. G. Mazzanti.