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*Presentation# AD13*

# Connecting Open-Source and Enterprise Software

## Enhancing Phase III Clinical Trial Design Through **R** Integration in **East Horizon™**

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# *Disclaimer*

The slides and views expressed in this presentation are those of speakers and are not representative of Cytel's views or opinions.

# Outline

Open-Source and Enterprise Software

East Horizon™ for Design of Clinical Trials

Motivation : Open-Source Integration in East Horizon™

R Integration in East Horizon™ – Workflow Demo

Conclusions

# Open-Source and Enterprise Software



- Highly Customized and Novel Analysis
- Open-Source Community Support
- Popularity with Statisticians

- Structure : Performance, Scalability, Security
- Vendor Accountability & Support
- Usability for Cross-Functional Team

# Open-Source and Enterprise Software

# East Horizon™ Explore:  for Design of Clinical Trials

DESIGNS → SCENARIOS → SIMULATION → OPTIMIZATION

## Provide Study Alternatives Through Designs

Strategic, **controllable aspects** of the trial e.g. *sample sizes, type I errors, choice of test statistics*.

## Manage Real-world Uncertainty With Scenarios

**Uncontrollable trial dynamics** e.g. effect sizes, enrollment and dropout rates and their *likelihoods*

## Simulate The Full Model Space

All models formed by **Scenarios × Designs** inputs are executed using simulation-based Engine.

## Find Optimal Design using Tradeoff Advisor (ToA)

**Heatmap, table** with clever **filters**

**Score** based on operating characteristics and relative weights

**Robustness** of design across scenarios

# East Horizon™ Explore:  for Design of Clinical Trials

For illustration, we consider a Phase III oncology trial to compare the efficacy of an investigational treatment against control using Overall Survival (OS) as the primary endpoint.

| | |
|---|---|
| **Trial Type** | Two-Arm Confirmatory |
| **Hypothesis** | Superiority |
| **Type I error** | ≤ 2.5% |
| **Sample Size** | ≤ 250 patients |
| **Study Duration** | ≤ 60 Months |
| **Target Power** | ≥ 80% |

| | |
|---|---|
| **Response** | Control Hazard Rate = 0.08, HR : 0.55 – 0.65 |
| **Dropouts** | Control = 5% , Treatment = 3%, by 10 Months |
| **Enrolments** | 20-30 patients per month |

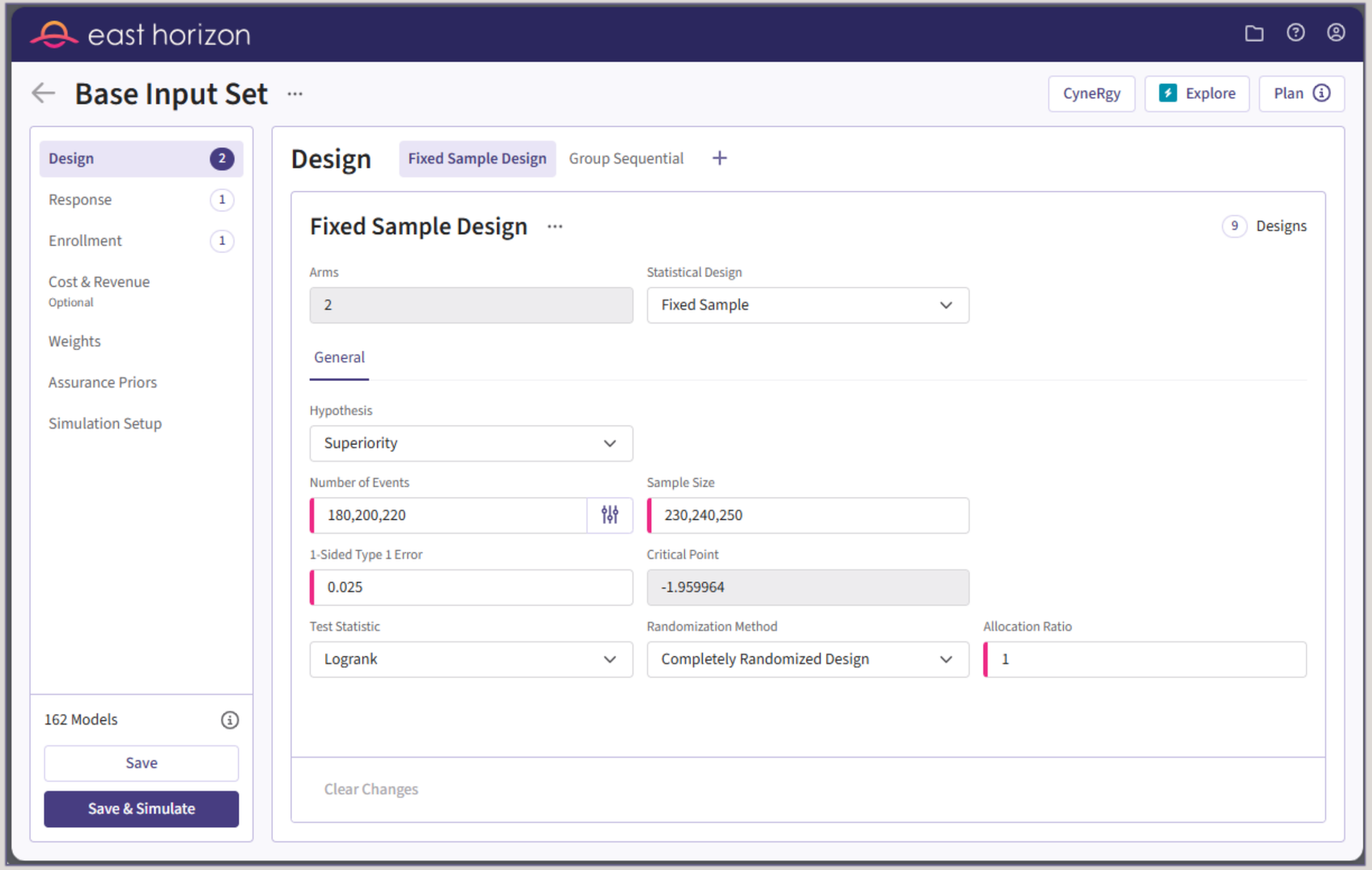
**Goal:** Select few candidate designs abiding to the requirements and operational/ regulatory constraints **across possible scenarios.**

# East Horizon™ Explore:  for Design of Clinical Trials

**DESIGNS**

## Provide Study Alternatives Through Designs

Strategic, **controllable aspects** of the trial e.g. *sample sizes, type I errors, choice of test statistics.*

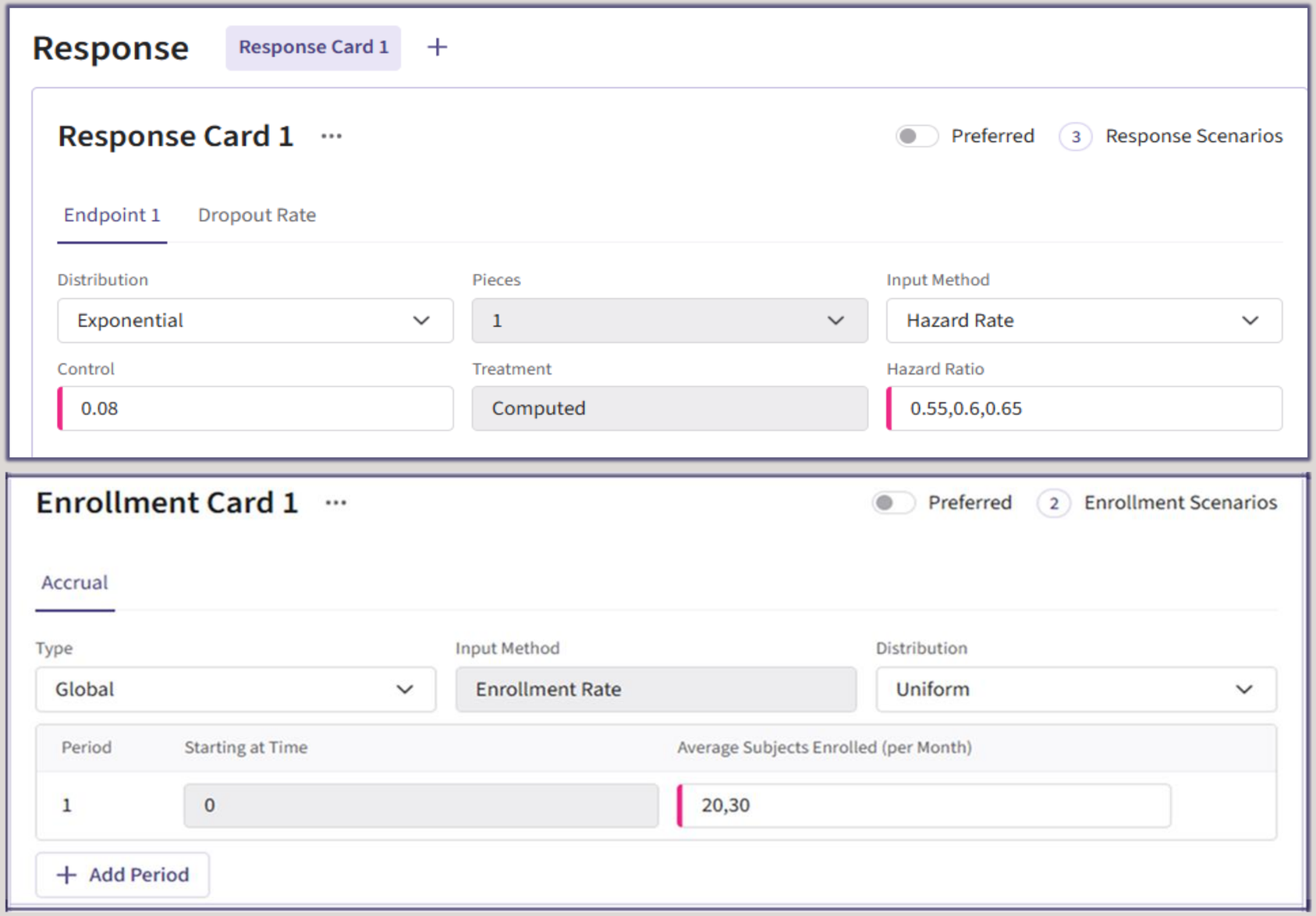


# East Horizon™ Explore:  for Design of Clinical Trials

SCENARIOS

## Manage Real-world Uncertainty With Scenarios

**Uncontrollable trial dynamics** e.g. effect sizes, enrollment and dropout rates and their *likelihoods*

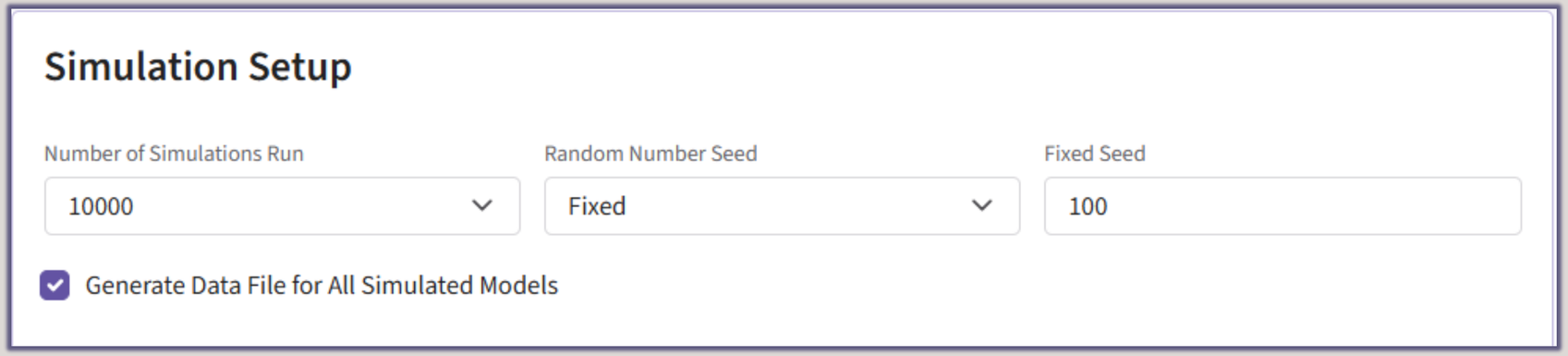


# East Horizon™ Explore:  for Design of Clinical Trials

SIMULATION

## Simulate The Full Model Space

All models formed by **Scenarios × Designs** inputs are executed using simulation-based Engine.




| Enrollment | Randomization | Response | Dropout | Analysis |
|---|---|---|---|---|
| Simulate patient accrual over calendar time. | Assign treatments according to trial design. | Generate the response values for the endpoints. | Generate dropout times/ CensorIDs etc | Compute effect size, test statistic and decision. |

# East Horizon™ Explore:  for Design of Clinical Trials

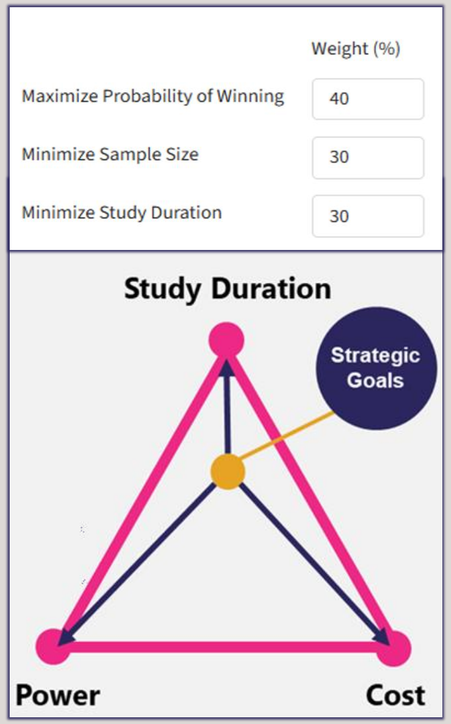
OPTIMIZATION

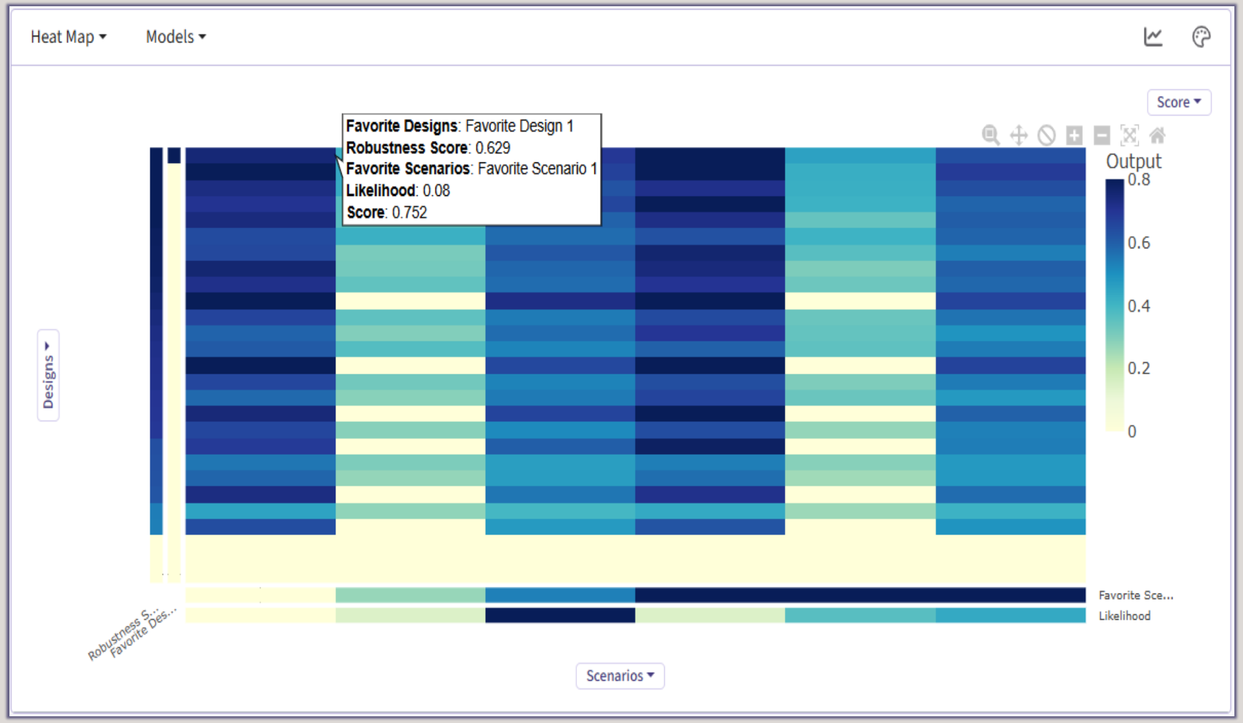
## Find Optimal Design using Tradeoff Advisor (ToA)

**Heatmap**, **table** with clever **filters**

**Score** based on operating characteristics and relative weights

**Robustness** of design across scenarios




| *Best Across All Scenarios* | *Wt. Power [Power]* | *Avg. SS Min - Max* | *Avg Study Duration Min - Max* |
|---|---|---|---|
| GSD, *Events* : 200, SS : 230 | ***91.46% [83.36% -98.46%]*** | ***218.97 – 229.13 patients*** | ***33.14– 38.19 months*** |

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# Motivation: Open-Source Integration in East Horizon™

## Expected Response

**Scenario 1:** Proportional Hazard

Control Hazard Rate = 0.08
Hazard Ratio : 0.6

**Scenario 2**: NPH : Delayed Effect-1

Control Hazard Rate = 0.08

| *Starting at time* | *0* | *6* | *9* |
|---|---|---|---|
| *Hazard Ratio* | *1* | *0.7* | *0.5* |

**Scenario 3**: NPH : Delayed Effect-2

Control Hazard Rate = 0.08

| *Starting at time* | *0* | *3* | *9* |
|---|---|---|---|
| *Hazard Ratio* | *1* | *0.7* | *0.5* |

# Motivation: Open-Source Integration in East Horizon™

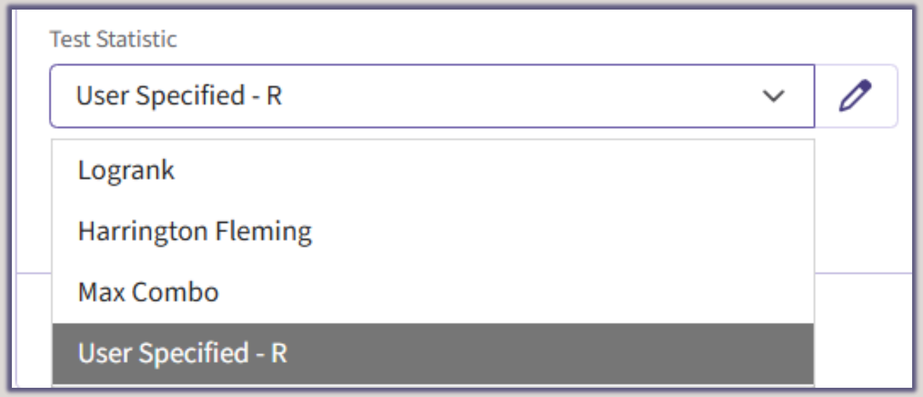
## Choice of Analysis:

***Modestly Weighted Log Rank (MWLR)*** test statistic (*Magirr, 2021*)

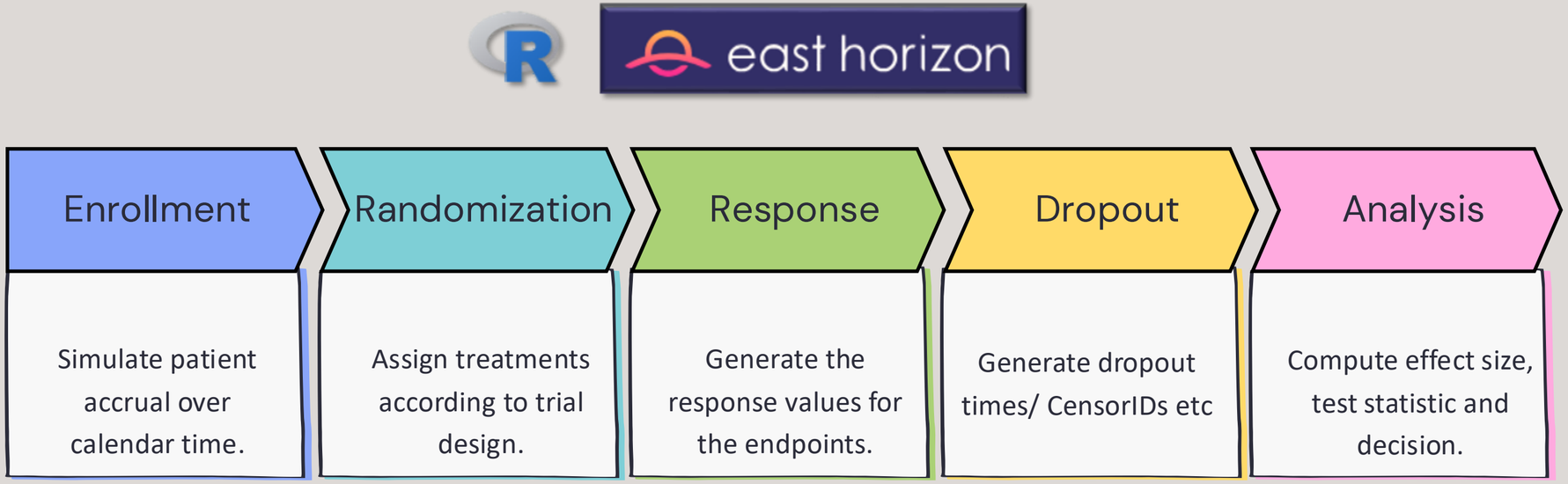
- Delayed Effect –> Higher Power
- Proportion Hazard –> Reasonable Power
- Better Type I Error Control than Harrington-Fleming Family

Not available **with East Horizon™.**

*Write a **R function** to compute MWLR test Statistic and let **East Horizon™** handle the remaining simulation flow.*



# R Integration in East Horizon ™ – Workflow Demo




***R Integration for :***

- *Custom, sophisticated methods*
- *Computing additional summaries.*
- *Harnessing power of **Tradeoff Advisor (ToA)***

# R Integration in East Horizon ™ – Workflow Demo

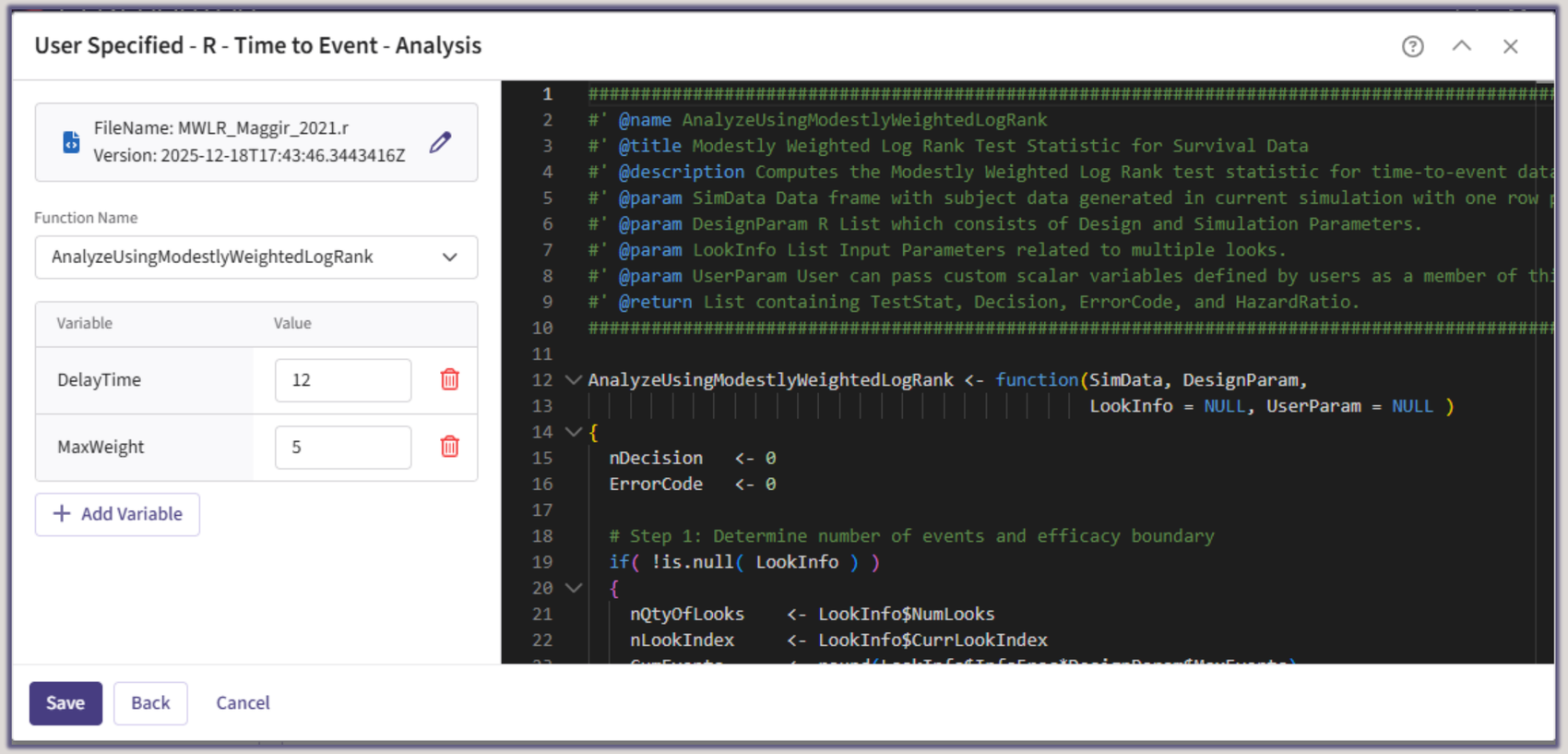
**Engine Inputs**
Native + Additional

```
AnalyzeUsingModestlyWeightedLogRank ← function( SimData, DesignParam,
                                                LookInfo = NULL, UserParam = NULL )
```

**Output List**
Optional + Mandatory

```
return( list( TestStat = as.double(dTS), Decision  = as.integer(nDecision),
              ErrorCode = as.integer(nError), HazardRatio = as.double(dTrueHR)) )
```

**Window for handling R inputs**
Script and UserParam inputs



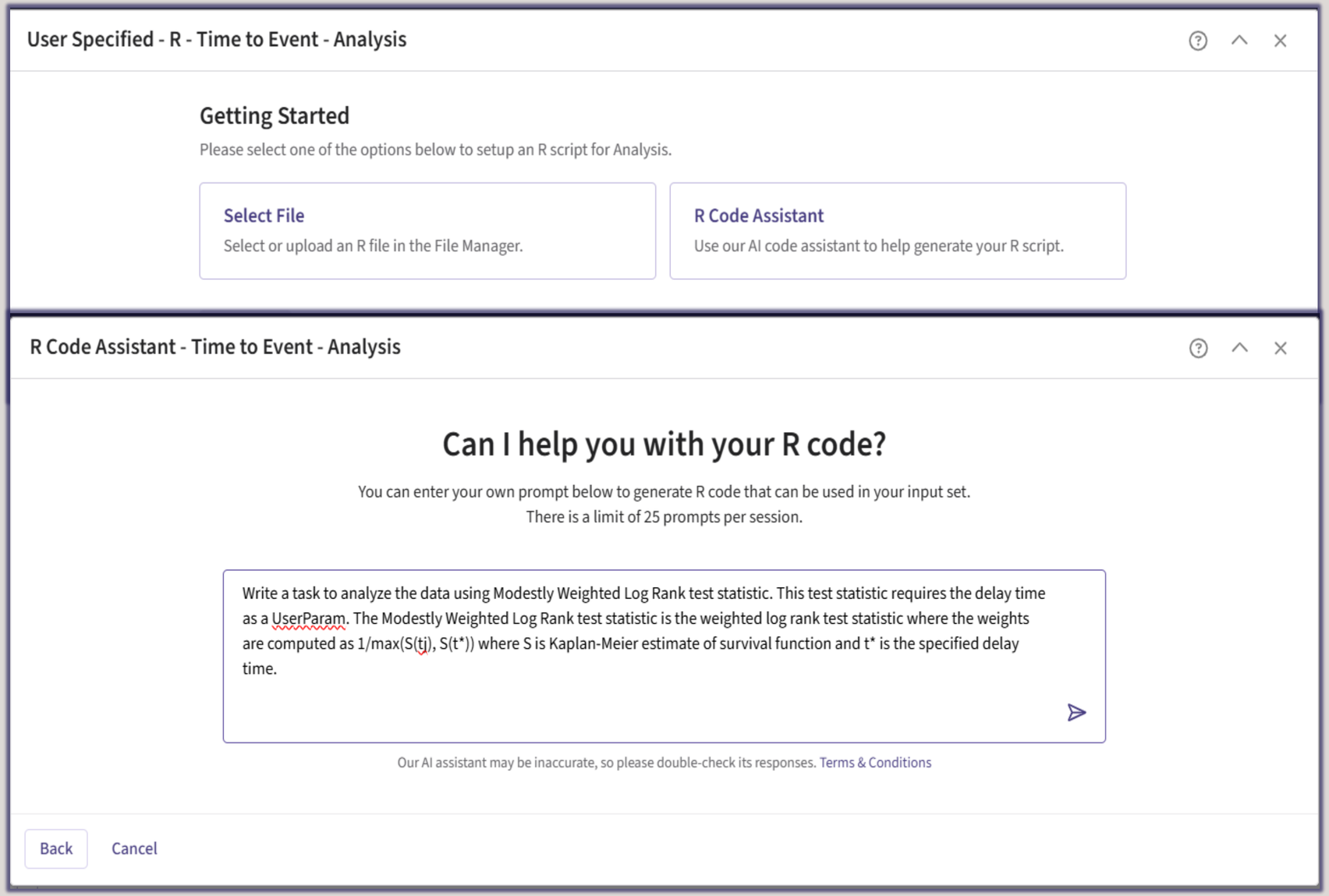
# R Integration in East Horizon ™ – Workflow Demo

**Select File**

Manual writing and uploading the R function.

**R Code Assistant**

Code generation in the prescribed format



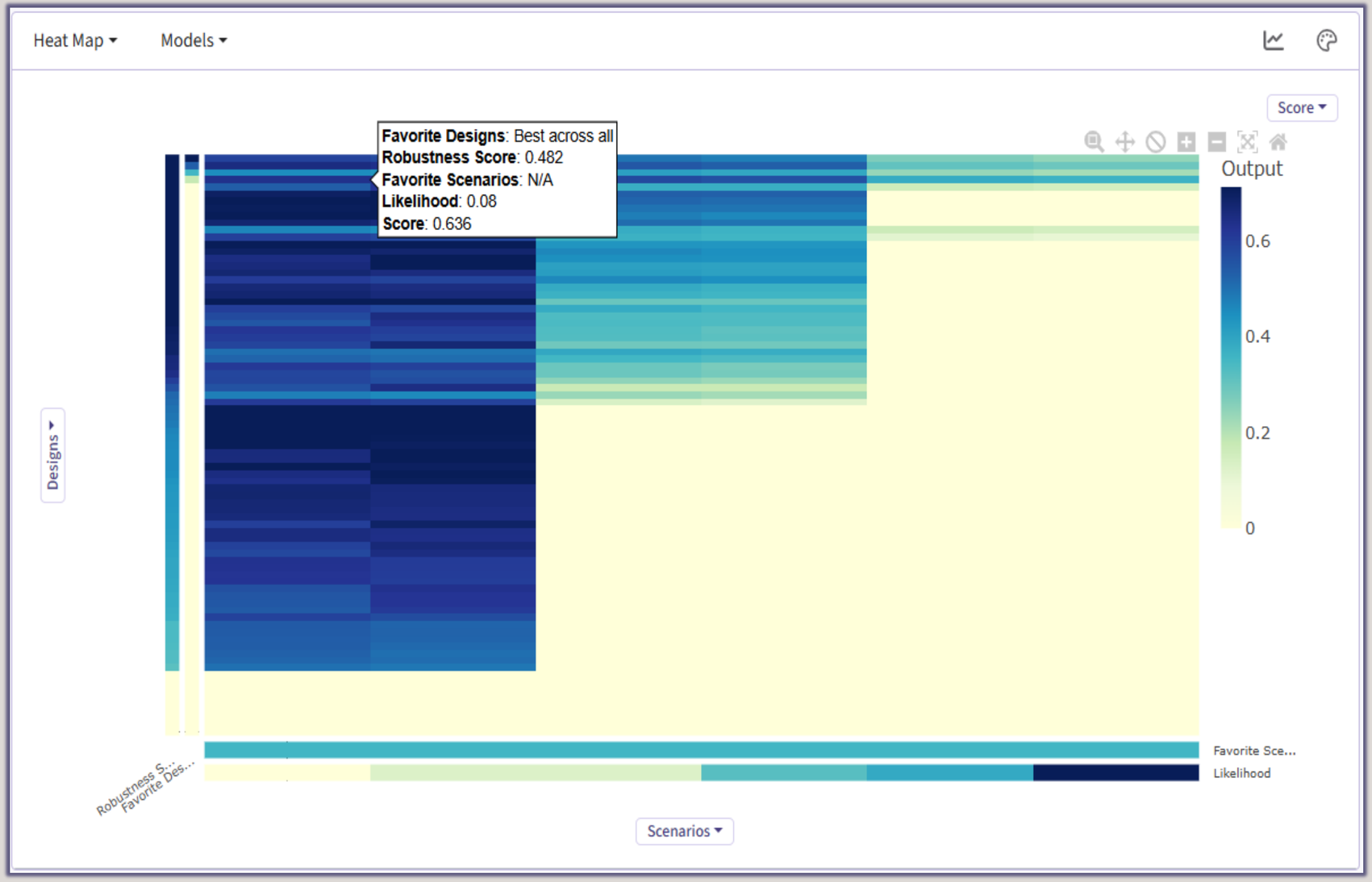
# R Integration in East Horizon ™ – Workflow Demo

### Test Statistics

*Log-Rank*
*MWLR (Delay= 9, MaxWt= 5)*
*MWLR (Delay=1 2, MaxWt= 5)*

### Simulations

*# of Designs : 81 (27 × 3)*
*# of Scenarios : 6 ( 3 × 2)*
*# of Models : 486 (27 × 6)*



# R Integration in East Horizon ™ - Workflow Demo

## Candidate Designs : Best Across All Scenarios

| *Original Weights* | *Wt. Power* *[Power]* | *Avg. SS* *Min - Max* | *Avg Study Duration* *Min - Max* |
|---|---|---|---|
| Fixed Sample , *MWLR (delay=12, MaxWt =5), Events* : 200, SS : 230 | ***87.94% [83.30% -93.84%]*** | ***230 patients*** | ***45.38– 49.09 months*** |

| *Maximum Power* | *Wt. Power* *[Power]* | *Avg. SS* *Min – Max* | *Avg Study Duration* *Min - Max* |
|---|---|---|---|
| Fixed Sample , *MWLR(delay=12, MaxWt =5), Events* : 220, SS : 250 | ***90.36% [86.32% -95.12%]*** | ***250 patients*** | ***48.56 – 52.81 months*** |

| *Minimum Study Duration* | *Wt. Power* *[Power]* | *Avg. SS* *Min - Max* | *Avg Study Duration* *Min - Max* |
|---|---|---|---|
| Fixed Sample , *MWLR(delay=12, MaxWt =5), Events* : 200, SS : 240 | ***85.97% [80.12% -93.91%]*** | ***240 patients*** | ***37.69– 41.23 months*** |

***Note:*** *Best* ***Minimum Sample Size*** *Design was found to be same as best* ***Original Weights Design.***

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# Conclusions

- **Open-Source + Enterprise Software : best of both worlds**
  - Structure & Validation
  - Flexibility & Community Support

- **Development of complementary tools: More accessible integration**
  - AI-powered assistance
  - Dedicated documentation/repository

- **East Horizon™ demonstrates this by Providing R – Integration points to Simulation components.**

# Thank you! Any questions?

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