Paper AD13

Connecting Open-Source and Enterprise Software: Enhancing Phase III Clinical Trial Design Through R Integration in East Horizon

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ABSTRACT

Enterprise software products have long provided a structured solution for designing clinical trials. However, some statisticians may find that software capabilities limit study design features and objectives. Recently, open-source tools have increased in popularity in clinical research. The flexibility and strong community support for open-source languages have positioned custom software development as an alternative to proprietary solutions. That said, developing standalone open-source software is fraught with limitations, such as increased development timelines, and code validation issues.

This paper outlines how integrating open-source tools with enterprise software offers the best of both worlds: flexibility and innovation alongside structure and regulatory compliance. We present a case study evaluating wider design and analysis options for a Phase III oncology trial, highlighting the benefits of a workflow that integrates R with the East Horizon platform, Cytel's enterprise solution for clinical trial design. As part of our paper, we will demonstrate this workflow and capabilities.

INTRODUCTION

Clinical trial design has traditionally relied on enterprise software environments that offer structured workflows, and built-in compliance features. These systems have served as the backbone for statistical planning across the industry, particularly in later-phase development. However, as trial designs become more sophisticated and therapeutic areas more complex, statisticians increasingly require analytical flexibility that extends beyond what conventional enterprise tools can accommodate.

At the same time, open-source ecosystems like R have rapidly expanded in both capability and adoption within clinical research. Their extensibility, reproducible programming paradigms, and thriving community support enable the development of highly customized analytical workflows. Yet, relying solely on open-source software introduces its own challenges, including fragmented development efforts, inconsistent validation expectations, and increased time required to bring new tools into production-ready states.

This evolving landscape has created a strategic opportunity to blend the strengths of both approaches. Integrating open-source tooling with enterprise software can deliver a "best of both worlds" model, providing innovation and analytical breadth without sacrificing structure, usability, or regulatory readiness.

In this paper, we present a working example of integrating **R** within **East Horizon™**, **Cytel**'s enterprise platform for clinical trial design. Using a Phase III oncology-inspired case study, we illustrate how this hybrid environment broadens design and analysis capabilities while preserving the quality, traceability, and governance required in regulated settings. The case study is methodological in nature: we use design parameters from a previously conducted trial solely as realistic inputs for simulation and workflow demonstration for trial planning.

EAST HORIZON™ FOR DESIGNING CLINICAL TRIALS

Designing a clinical trial is a complex and critical undertaking. Inadequately designed trials may fail to demonstrate a true clinical benefit or may prove inefficient from ethical and economic perspectives. Trial planning must account for a range of factors, both uncontrollable and controllable. Uncontrollable factors include uncertainty in treatment effects, as well as variability in enrollment rates and dropout patterns. Controllable factors encompass key design choices such as the study design, sample size, type I error allocation, and analysis methodology. The objective of prospective design evaluation is to identify combinations of these controllable parameters—referred to as *designs*—that satisfy operational constraints (e.g., sample size and study duration) while maintaining the desired statistical power.

East Horizon™ is an enterprise-level platform from Cytel designed to support rigorous and efficient clinical trial design. The **Explore** module within East Horizon incorporates a simulation-based engine along with advanced optimization capabilities that enable the identification of statistically and operationally optimal designs from a large and complex model space. This ability to systematically evaluate and extract optimal solutions is a key factor underlying the platform's strength.

In *Explore*, the *model space* is defined as the Cartesian product of *designs*, representing choices of controllable factors and *scenarios*, which correspond to assumptions about uncontrollable factors. This framework enables comprehensive evaluation of operating characteristics across a wide range of plausible trial conditions.

Full model space is evaluated using a powerful, cloud-based simulation engine. For each model within this space, key operating characteristics including statistical power, expected treatment effect, average study duration, and average sample size—are estimated and presented to the user for detailed review and comparison. *Figure 1* illustrates the simulation workflow in East Horizon™ used to evaluate each specified model across a predefined number of simulations runs.

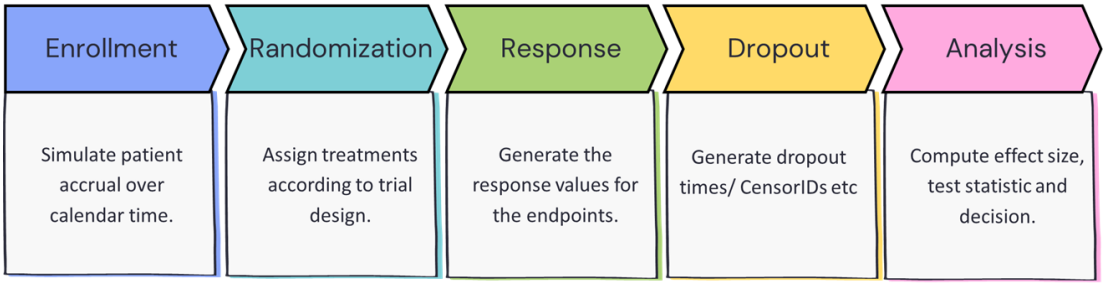

Figure 1: East Horizon ® Simulation flow

The primary objective is to identify a small set of candidate designs that are optimal under predefined criteria while satisfying statistical requirements (e.g., at least 80% power) and operational or ethical constraints (e.g., maximum sample size of 250 subjects and a study duration not exceeding 60 months). Importantly, the key operating characteristics of a clinical trial—power, study duration, and sample size—are inherently subject to trade-offs. A single design that simultaneously optimizes all three metrics is generally not feasible. Consequently, one has to specify relative weights for these criteria, constrained to sum to one, to reflect their comparative importance and guide the order the designs as per this weighted score.

The **Tradeoff Advisor** is a visualization-driven decision-support tool designed to facilitate exploration and comparison across the full model space (designs × scenarios). It provides multiple interactive visualizations—including heatmaps, radar plots, and parallel coordinate plots—to represent key operating characteristics such as score, statistical power, average sample size, and average study duration. In addition, Tradeoff Advisor offers advanced filtering capabilities across both input parameters and resulting operating characteristics. Together, these features make Tradeoff Advisor an efficient and powerful tool for narrowing the model space and identifying candidate trial designs. *Figure 2* illustrates a Tradeoff Advisor heatmap summarizing a model space of 162 models.

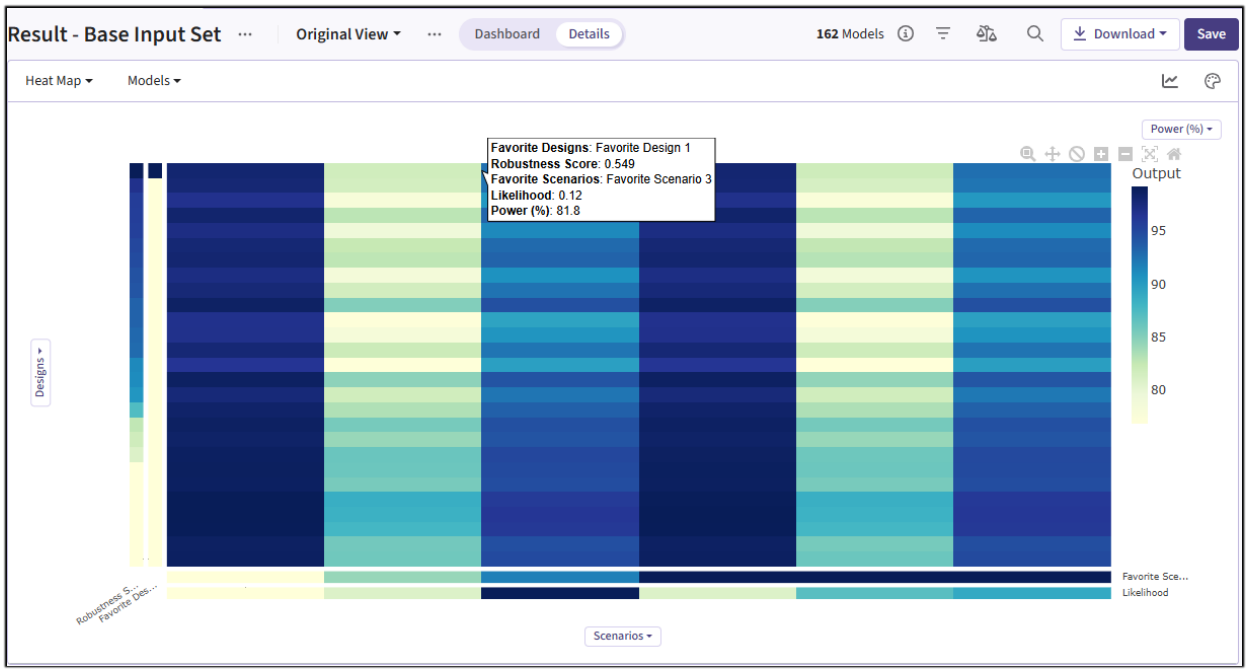

Figure 2: Tradeoff Advisor (ToA) representing model space of 162 models as a Heatmap

THE MOTIVATING EXAMPLE

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. The trial is designed to test a superiority hypothesis with a target power of at least 80% and a one-sided type I error rate of 2.5%. The trial has operation constraints: a maximum sample size of 250 patients and a maximum study duration of 60 months.

The key uncertainty assumptions include expected dropout rate of 5% in the control arm and 3% in the treatment arm by 10 months, enrollment expectation with uniform rate of 20-30 patients per month and expected hazard behavior as mentioned in *Table 1*. The objective of this case study is to identify a small set of candidate trial designs that satisfy the statistical requirements while adhering to operational and regulatory constraints, accounting for inherent trade-offs among power, study duration, and sample size.

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*

Table 1: Expected Response Scenarios

Two of the three response scenarios considered in this case study suggest the presence of a delayed treatment effect and therefore violate the proportional hazards assumption. Under such conditions, the standard log-rank test may be suboptimal. The Modestly Weighted Log-Rank (MWLR) test proposed by Magirr (2021) represents a suitable alternative, as it offers increased power relative to the log-rank test in the presence of delayed effects, remains reasonably efficient under proportional hazards, and provides improved type I error control compared with the Harrington-Fleming family of weighted log-rank tests. At present, the MWLR test statistic is not natively available within East Horizon™; however, the **Analysis R integration** point can be utilized to incorporate a custom R implementation of the MWLR test.

R – EAST HORIZON™ INTEGRATION – WORKFLOW AND CAPABILITIES

Although this paper focuses on the Analysis integration point, East Horizon® also supports such extensions through well-defined integration points across all major simulation components, including enrollment, randomization, response generation, dropout, and analysis. This flexible architecture enables users to incorporate advanced or non-standard methodologies—such as novel analysis techniques or complex response models—via custom R implementations, while continuing to leverage East Horizon™ for the overall simulation orchestration and its powerful Tradeoff Advisor functionality.

The R function that will be provided through the integration points need to follow input and output signatures specified for that integration point. *Figure 3* shows the signatures required for analysis integration task. Cytel is maintaining a *dedicated R – package* - **CyneRgy** and corresponding website help user with tools, documentation, templates, and examples while writing these examples.

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

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

Figure 3: Input (upper) and output signatures for R Analysis Task

While it is extremely critical to follow this signature to correctly communicate the information across other simulation components, that can be a lot of cumbersome. To improve accessibility of the integration framework, an **AI-powered R Code Assistant** has been introduced. The assistant can generate R function implementations in the required

format from natural language prompts and supports multi-step, conversational refinement within a single session. In addition, it includes an in-place R execution environment with synthetic data to enable validation and testing of the generated code. *Figure 4.1* shows the R Code Assistant input window, whereas *Figure 4.2* shows an output window with in-place R code execution option.

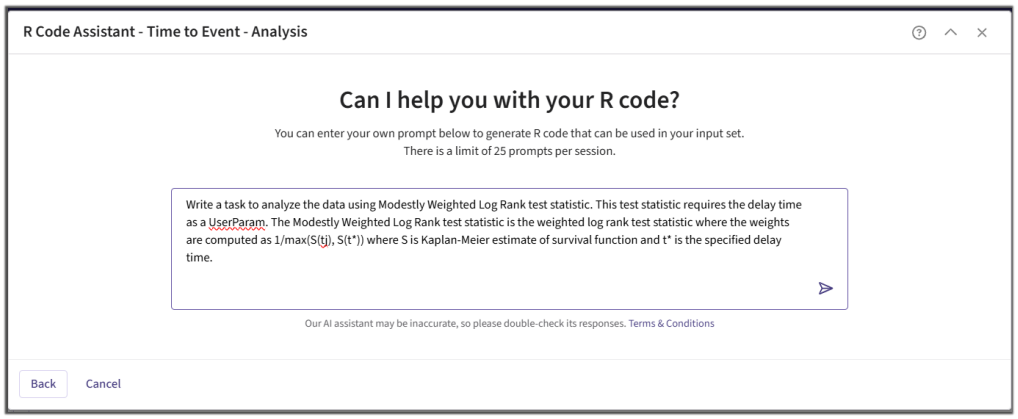

Figure 4.1: R Code Assistant: Specifying Prompt

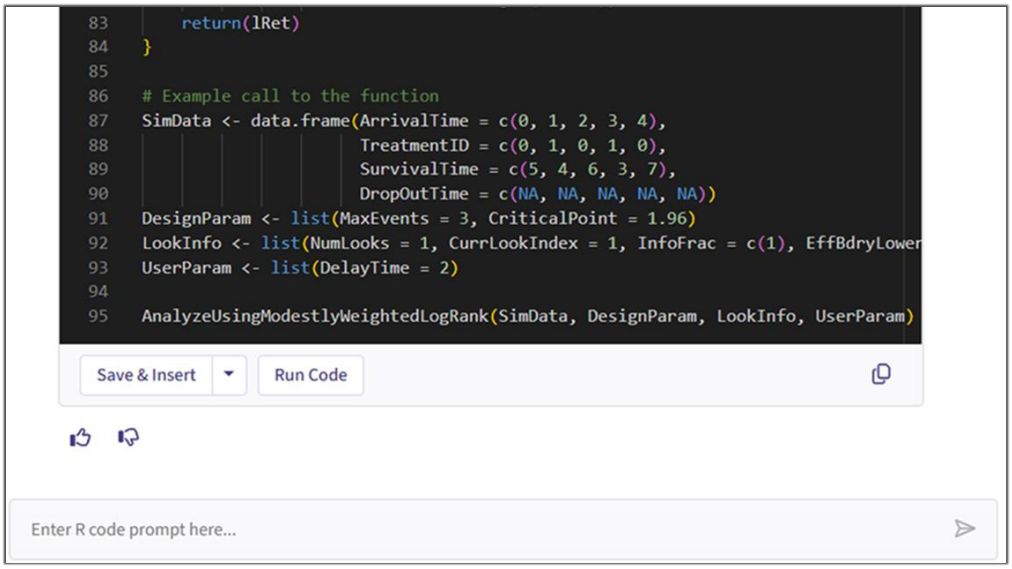

Figure 4.2: Provision for in-place validation of generated code

Errors in custom R code—whether written manually or generated using the Code Assistant—are common and must be effectively diagnosed. When a simulation fails due to integrated R code, East Horizon™ records the relevant error messages in the simulation log. In addition, the executed R script and the input data passed to the function are saved in RDS format. This allows users to reproduce the issue outside the platform and debug the code efficiently. See, *Figure 5*.

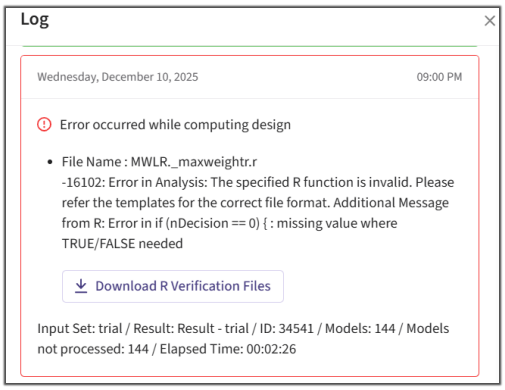

Figure 5: Error message along with link to download files for debugging

SIMULATION OF THE EXAMPLE TRIAL

As part of the R – East Horizon® integration demonstration, we evaluated the power and other operating characteristics of a example mentioned above.

SETUP OF THE DESIGN

- Design : *Fixed Sample, Group Sequential (1 interim at 50% Info, LD-PK spending function)*
- Type I Error : *0.025*
- Target Events : *180, 200, 220*
- Sample Size : *230, 240, 250*
- Test Statistic : *Log-Rank, MWLR(Delay=9, MaxWt=5), MWLR(Delay=12, MaxWt=5)*
- # simulation runs : *10000*

ORIGINAL SCORING WEIGHTS AND CONSTRAINTS

- Maximize Power : *Weight – 40%, Threshold (>.8)*
- Minimize Sample Size : *Weight – 30%, Threshold (≤ 250)*
- Minimize Study Duration : *Weight – 30%, Threshold (≤ 60)*

SCENARIO AND WEIGHTS

- Enrollment : *Rate: 20 patients/month* : *Weight – 60%*
  : *Rate: 30 patients/month* : *Weight – 40%*
- Response : *Proportional Hazard* : *Weight – 20%*
  : *Delayed Effect 1* : *Weight – 50%*
  : *Delayed Effect 2* : *Weight – 30%*

SIMULATION RUN AND RESULTS

Using the Tradeoff Advisor (ToA), three designs were selected from a set of 81 candidate designs (See *Table 2*). These designs were identified under different optimality criteria by assigning different relative weights to the operating characteristics. The resulting trade-offs among key metrics are evident. For example, if we choose 'Maximum Power' design over the design with 'Original Weights', the gain in power is accounted for by increase in Avg. Sample Size and Avg. Study Duration.

Similarly, loss of power is observed by choosing 'Minimum Study Duration' design over 'Maximum power' design or 'Original Weights' Design. It was also observed that the 'Original Weights' Design is the one yielding 'Minimum Sample Size'.

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.***

Table 2 Simulation Results: Selected Candidate Designs

CONCLUSION

The example presented in this paper illustrates how integrating open-source tools with an enterprise platform such as East Horizon® can offer a powerful combination of flexibility, structure, and regulatory readiness. This hybrid approach allows statisticians to incorporate custom methodologies while still benefiting from the governance and reproducibility of an enterprise environment. In addition, features such as the coding assistant, debugging support and *CyneRgy* reference package make it easier for users to develop and implement custom R functionality, reducing effort and accelerating the design process. Together, these capabilities demonstrate the value of a connected workflow that blends innovation with the reliability required for clinical trial planning.

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