CERTARA

Certara Trial Simulator v2.3

Powerful, Flexible, and Intuitive

Are Trial Failures Preventable with Better Design?

9 out of 10 drugs in development fail to make it to market, costing pharmaceutical companies billions every year.[1] Even the majority of drugs that get to Phase 3 do not get approved.[2] These late stage failures are especially costly as companies have already invested hundreds of millions of dollars in discovery, development, research, and testing.[1]

One reason for trial failures is suboptimal trial design.[1,2] There are many variables to fine tune to optimize study design and maximize probability of trial success. Certara's Trial Simulator® has been trusted for over a decade by leading pharmaceutical companies to maximize their chances of success. Leveraging existing knowledge for a drug under study with simulation, you can find answers to critical questions like:

- How likely is a trial to succeed?
- What is the optimal dosing and treatment schedule for a particular indication?
- What is the expected range of responses across doses?
- How will a change in inclusion/exclusion criteria affect outcomes?
- How frequently should the response be measured?
- What is the impact of poor compliance or concomitant disease?
- Should drug development be stopped if the results might not support a competitive drug?
- Can we shorten Phase 1 and Phase 2 clinical trials?
- Can we reduce the cost of the next trial?
- Will the drug be successful in Phase 3?

Your First Choice for Computer-assisted Trial Design

Trial Simulator provides a more efficient approach to computer-assisted trial design. Its robust tools support a user in:

- Defining study design attributes
- Conducting statistical and sensitivity analysis
- Creating graphical summaries

This enables an entire drug development team to improve access to existing scientific knowledge, communicate and test ideas, and plan relevant, effective trials for every phase of clinical drug testing.

The flexibility and ease of use of Trial Simulator empower both the novice and more advanced users. It provides an intuitive user interface and step-by-step approach to help new users learn trial simulation with ease. For more complex trial situations, it has tremendous flexibility and versatility.

You can anticipate risks and preview the range of expected results before millions in R&D dollars are spent and human subjects are exposed to experimental therapies.

What's New in Trial Simulator v2.3

- *Works on Windows® 7 SP1, 8.1, and 10*
- *Connects seamlessly with R for custom plot capabilities*
- *Is 100% backward compatible with previous version of Trial Simulator*

Key Features

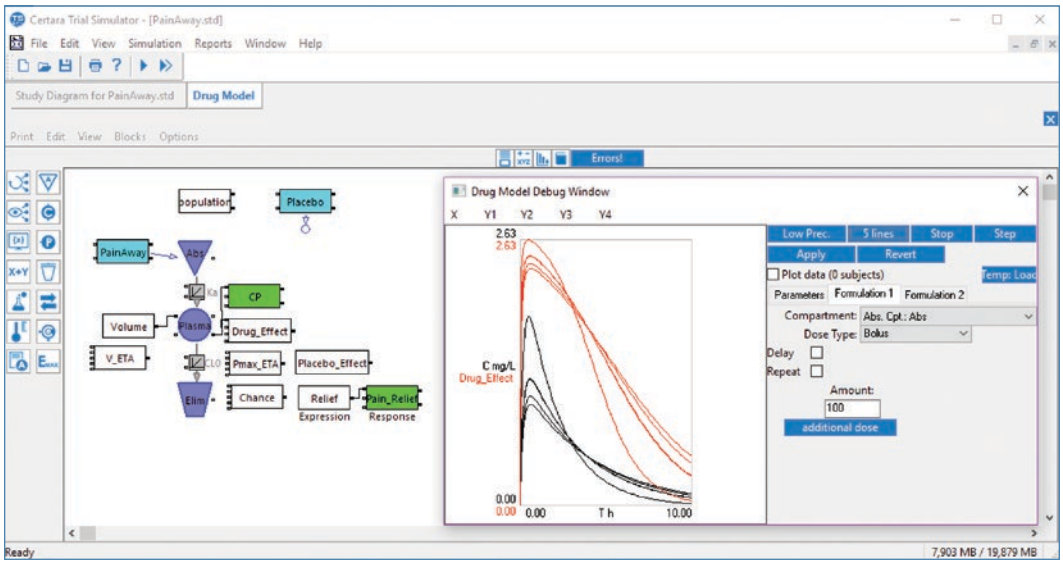
- Component-driven, modern, graphical interface for rapid, flexible model building
- Ability to create novel study designs and compare different development strategies
- Extensive library of pre-built PK, PK/PD and PBPK models
- Intuitive expression editor with built-in functions for including userwritten expressions or differential equations
- Debugging tool that provides real-time plots of any variables in the drug model, including concentration and effects over time
- Descriptive statistics on input and output data including weighted descriptive statistics
- Built-in analysis routines including descriptive statistics, ANOVA, ANCOVA, bioequivalence analysis, and Kaplan-Meier survival analysis
- Plots generated in R and ggplot2 with custom plotting capabilities
- Ability to export data to Excel-ready files, Phoenix WinNonlin, Phoenix NLME, SAS, NONMEM, and R

Comprehensive Modeling of Drug Action

With Trial Simulator, you can build population-based drug, disease models that describe drug actions over time in individual subjects. The drug model is created graphically by adding and connecting model blocks to define functions of subject characteristics, treatments and formulations, drug and disease actions, placebo effects and random factors.

This patented (US Application No. 7,043,415), component-driven, modern, graphical user interface allows you to easily specify attributes such as distributions of patient population variables, dosing and observation time and compliance variations. Estimates of compliance, measurement errors, and biological variability can be included. To save time, common PK, PK/PD and physiologically-based PK models are provided pre-built. You can also include written expressions or differential equations using a simple expression language or custom FORTRAN code, providing enhanced flexibility. Powerful debugging tools such as real-time plots of model outcomes, current equations for the drug model, and error messages for custom expressions and statements help you test and improve the drug model. Drug models can be shared by saving in XML or text format.

Drug Model and Debug Window for PainAway Dose-ranging Study (included in Trial Simulator)



Protocol Design

Trial Simulator supports a wide variety of trial designs, including parallel, n-by-n Latin square, and crossover designs with any number of treatment groups and periods. The study enrolls subjects from one or more study centers, each of which may draw subjects from a different subpopulation with different covariate distributions. Subjects may be screened for trial inclusion based on covariate values and/or responses measured during an optional lead-in phase. Active phase treatments and observations may include any number of doses and measurements, scheduled at specific times or using a recurring cycle of times. Trial Simulator supports adaptive dosing schemes and covariate or response based dose adjustments.

Deviations from the nominal protocol, ie, adherence, can be modeled as a one- or two-coin model for missing doses and observations, or as a deviation from scheduled dose or observation time. A protocol report is available for printing directly to a printer or to Microsoft® Word®. It includes all protocol settings, a graphical timeline of the protocol, and a table of scheduled events.

Integrated Study Analysis Plans

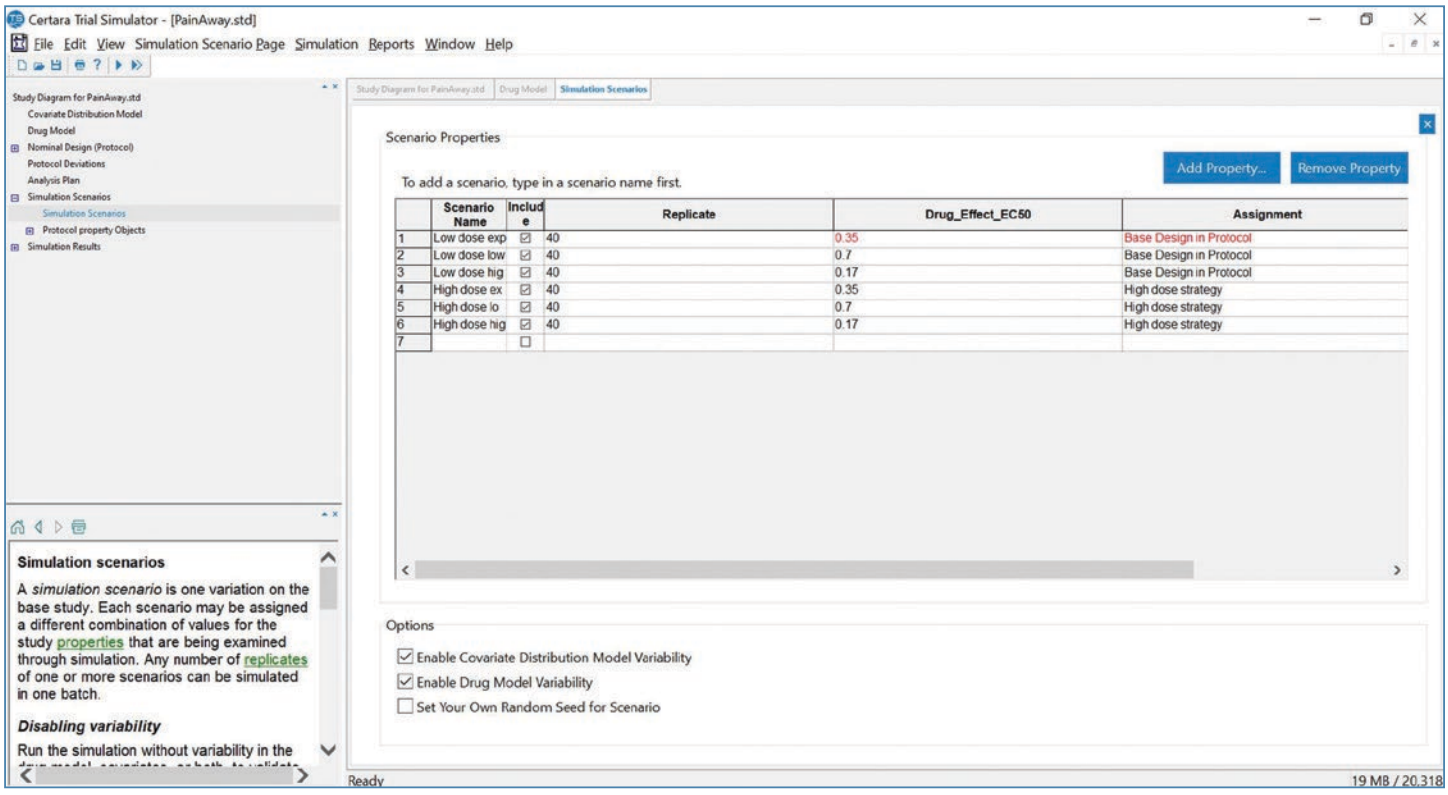
Trial Simulator's robust statistical and graphical analysis capabilities give you the ability to define study analyses and save results for meta-analysis after simulation. Built-in study analysis methods include descriptive statistics, ANOVA, ANCOVA, bioequivalence analysis, and Kaplan-Meier survival analysis. These methods can analyze outcome variables from Response blocks defined in the drug model and observed in the protocol, as well as unscheduled events and dropouts. The analysis plan can also include creation and analysis of calculated field variables and supports missing or below quantifiable-limit data handling. Missing data points can be excluded from analysis or replaced with the last observed value carried forward to the end of the study for a given subject. A report that summarizes the data analysis plan can be printed or automatically generated in Microsoft Word.

Simulation Scenario "What If" Comparisons

A simulation scenario, a variation on a model and trial design, is used to test the impact of model assumptions and protocol design choices. Any number of scenarios are simulated multiple times to estimate the distribution of potential outcomes for each. By exploring and analyzing simulation results over a range of assumptions and design parameters, the development team can pinpoint clinical trial designs that are optimized for robustness against uncertainties. Uncertainty of model parameters can be simulated at the study level, and Trial Simulator also supports model uncertainty where you can have several different variations of the model in simulation scenarios.

The Scenario Properties Table is used to create the automated simulations. Within the table, any number of scenarios can be defined, and options for running the simulation can be selected. Simulation options include enabling population variability, drug model variability, and control over random number seeds used to generate the variability.

Scenario Properties Table for PainAway Study



Simulation Results Analysis

Cross-replication analysis and scenario comparisons are done using the Simulation Results component of Trial Simulator. Plots, exports, and analyses may be performed on the whole database or on a specific subset of the database. The Results page of a study provides features to view, sort, filter, plot, analyze, and export data. Grid views display selected data in an easy-to-read, table-like form. Analyses include summary statistics and descriptive statistics, ANOVA/ANCOVA and bioequivalence analysis, Kaplan-Meier survival analysis, and custom R analysis. Plots may be made on any selected data using the Plot Wizard. You can also export simulated trial results to other analysis tools such as Phoenix WinNonlin®, Phoenix NLME™, SAS®, NONMEM®, and R.

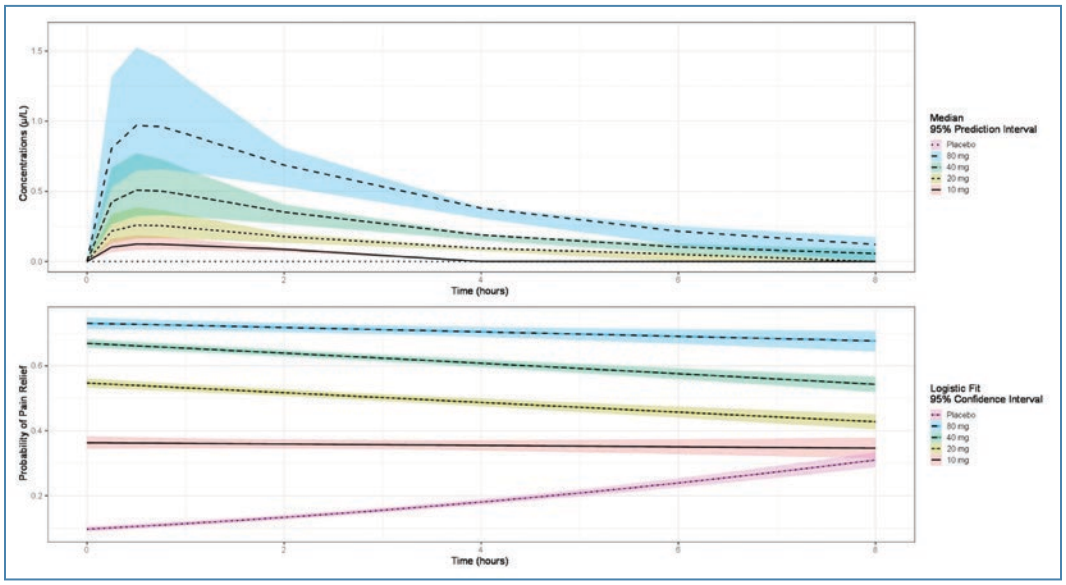
Recommended Requirements

	Minimum Recommended	Optimal Recommended
Processor	Intel i5, 3GHz	Intel i7, 4 GHz
RAM	8 GB	16 GB
Internal storage device	1 GB, 7200 RPM magnetic hard drive	1 GB Solid state drive (SSD)

Operating Systems
Windows® 7 SP1 or later (32- and 64-bit*)
Windows 8.1 (32- and 64-bit*)
Windows 10 (32- and 64-bit*)

* A 64-bit OS is recommended for systems with RAM > 4 GB

Example of Plot Using R and ggplot2



References

1. Lo C. (2017, June 19). *Counting the cost of failure in drug development.* Retrieved from https://www.pharmaceutical-technology.com/features/featurecounting-the-cost-of-failure-in-drug-development-5813046/

2. Grignolo A & Pretorius S. (2016, August 1). *Phase III trial failures: Costly, but preventable.* Retrieved from http://www.appliedclinicaltrialsonline.com/phase-iii-trial-failures-costly-preventable

For more information or to schedule a demo, contact sales@certara.com.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.