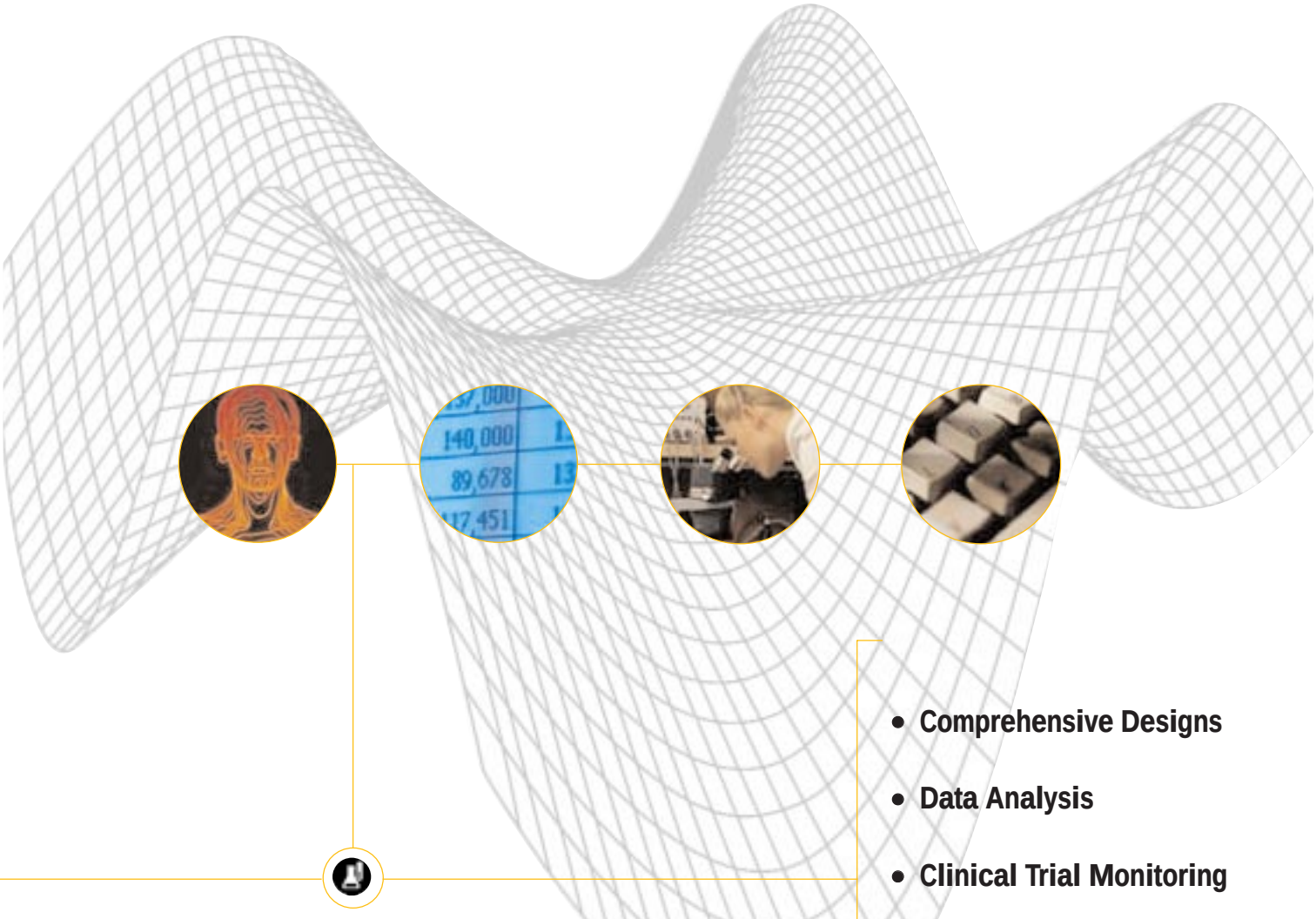
The Premier Software Package for the Design and Analysis of Clinical Trials

S-PLUS®

S+SeqTrial®



- Comprehensive Designs
- Data Analysis
- Clinical Trial Monitoring
- Validated Techniques
- Reduce Trial Costs

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S+SeqTrial—Bring Beneficial Treatments to Market Sooner

Reduce Clinical Trial Costs

Each year, the global pharmaceutical industry spends at least $10 billion on clinical trials and thousands of test patients are treated with experimental therapies. Typically, these trials are run using fixed sample designs, meaning all of the data must be collected before a decision can be made.

Group sequential designs allow researchers to monitor a trial throughout the data collection process, allowing studies to be terminated sooner, potentially saving the industry tens of millions of dollars by improving clinical trial efficiency, reducing the number of human subjects required, and optimizing scarce research resources. By stopping clinical trials early, beneficial treatments get to market sooner, and test subjects are spared further exposure to ineffective therapies.

> *"S+SeqTrial is the perfect tool for designing and monitoring clinical trials including a comprehensive selection of validated designs integrated with powerful data analysis capabilities. Its easy-to-use graphical user interface and professional graphics are ideal for communicating results to nonstatisticians and FDA reporting. S+SeqTrial will help our company to make decisions to terminate or continue trials sooner potentially saving lives and reducing clinical trial costs."*
>
> **Gracie Liebermann**
> Genentech

Introducing S+SeqTrial

S+SeqTrial is an S-PLUS software library for designing, monitoring, and analyzing clinical trials using *group sequential* methods. In a classical fixed sample design, the sample size is set in advance of collecting any data. The main design focus is choosing the sample size that allows the clinical trial to discriminate between the null and alternative hypotheses, thereby answering the scientific questions of interest.

In sequential design, data are monitored throughout the collection, and a decision to stop a trial can be made before all the data are accrued. In classical sequential studies, tests would be conducted after collecting every data point. The term group sequential refers to sequential studies in which the data are analyzed periodically, after a block of data is accrued. Group sequential designs are especially important for the design of Phase II and Phase III clinical trials, where ethical considerations such as patient safety and rapid approval of effective treatments are paramount. Indeed, the FDA now recommends group sequential studies in certain cases.

The Comprehensive Clinical Trial Solution

Improved Study Design

- Reduce costs and bring drugs to market sooner with sequential studies
- Interactive interface makes it easy to explore tradeoffs between designs

Comprehensive Design and Evaluation Tools

- Sequential designs in unified family of Kittelson and Emerson, including all commonly used group sequential designs
- Family of designs based on error spending function of Lan and DeMets
- Comprehensive evaluation tools, including power, conditional power, sample size distribution, inference at the boundaries, and Bayesian analyses

Completely Extensible

- Powerful S language for extending functionality to fit your needs; from small to large projects, from simple to complex analyses

Flexible Monitoring Methods

- Implementation of stopping rules based on error spending functions or constrained boundaries

Easily Analyze and Interpret Your Results

- Exact *p*-values
- Exact confidence intervals
- Bias adjusted estimates of treatment effect

Easy to Learn

- State-of-the art GUI (Graphical User Interface) documentation designed for the clinical trialist
- Fully integrated with S-PLUS data analysis software

Advanced Visualization Tools

- Comprehensive set of specialized plots for designing studies, including power curves, ASN (average sample size) curves, and stopping probabilities
- Trellis graphics for powerful and effective comparison of designs

Powerful Validation Techniques

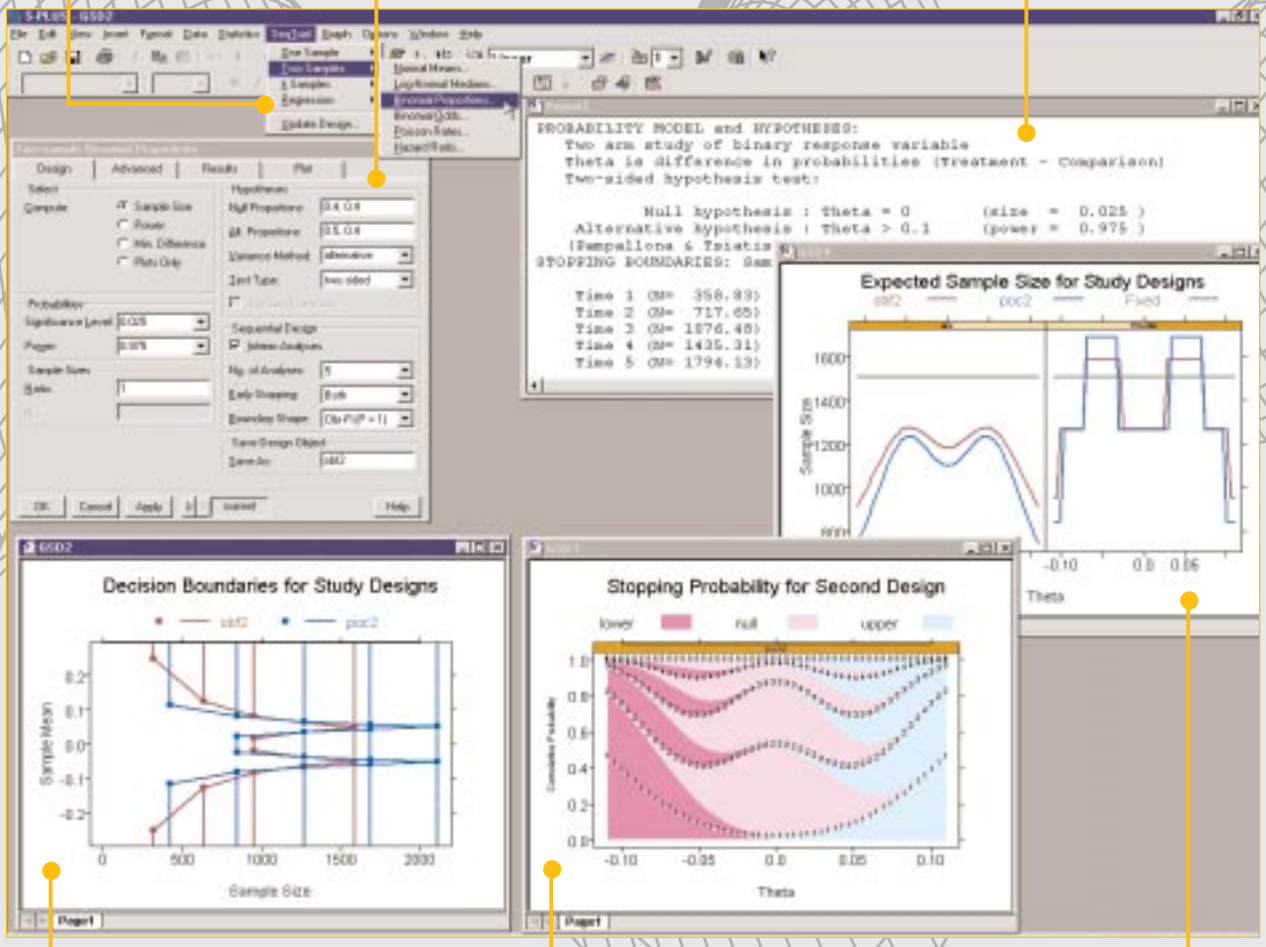
- Results validated against standard designs in the group sequential literature

Interactively Compute, Evaluate and Compare Clinical Trial Designs

Convenient Pull Down Menu: Select probability models according to study structure and type of outcome.

Easy to Use Graphical User Interface: Select specifications for comparison on-the-fly. An extensive properties dialog for both common and advanced designs makes it simple to compare models. The plots tab offers common plots with a selection of other designs for comparision, including: stopping boundaries, average sample number curve, power functions and stopping probabilities.

Convienent Report Window: Easily see tabular output of stopping boundaries, tables of power, sample size distribution, inference at the boundaries.



Display of Boundaries Plot: Visualize a variety of boundary test statistics, display multiple designs and compare thresholds for early stopping.

Stopping Probability Plot: Graphically display stopping probabilities and statistical decisions at each analysis time as a function of true treatment effect.

Sample Size Distribution Plot: Allows you to compare average sample size as well as quantiles of sample size distribution among candidate designs as a function of treatment effect. By also comparing the power curves, you can assess tradeoffs between early stopping and statistical power.

S+SeqTrial Features

A Complete Software Environment

- A fully object-oriented language with specialized objects (such as design objects, boundary objects, and hypothesis objects) and methods (such as operating characteristics and power curve plots)
- Full integration into the S-PLUS language for customized analyses, allowing you to extend S+SeqTrial as your applications demand
- An intuitive graphical user interface oriented towards both the clinical trialist and the statistician
- Many low-level routines for specialized analyses: for example, densities and quantiles
- An open software design with well-defined building blocks
- Easy comparative plots of boundaries, power curves, average sample number (ASN) curves, and stopping probabilities
- User-selected scales for boundaries: sample mean, z-statistic, fixed sample p-value, partial sum, error spending, Bayesian posterior mean, and conditional and predictive probabilities for stochastic curtailment
- Publication quality graphics based on the powerful Trellis Graphics system (Cleveland, 1993; Becker & Cleveland, 1996)

Stopping Rule Computation

- The unified family of group sequential designs, which includes all common group sequential designs: Pocock (1977), O'Brien & Fleming (1979), Whitehead triangular and double triangular (Whitehead & Stratton, 1983), Wang & Tsiatis (1987), Emerson & Fleming (1989), and Pampallona & Tsiatis (1994)
- A new generalized family of designs. S+SeqTrial includes a unified parameterization for designs, which facilitates design selection, and includes designs based on stochastic curtailment, conditional power and predictive approaches
- Applications including normal, binomial, Poisson, survival, one-sample and two-sample
- One-sided, two-sided, and equivalence hypothesis tests, as well as new hybrid tests
- Specification of the error spending functions of Lan & DeMets (1989) and Pampallona, Tsitais, & Kim (1993)
- Arbitrary boundaries allowed on different scales: sample mean, z-statistic, fixed sample p-value, partial sum, error spending, Bayesian posterior mean, and conditional and predictive probabilities
- Exact boundaries computed using numerical integration

Design Evaluation

- Power curves
- Maximal sample size calculations
- Sample size distributions: ASN curves and quantile curves
- Stopping probabilities
- Conditional power
- Statistical inference at the boundaries
- Bayesian properties (normal prior)
- Simulation from specified stopping rules

Monitoring Clinical Trials

- Adjust analysis times and boundaries to maintain specified size and power
- The exact error spending approach of Lan & DeMets (1989) and Pampallona, Tsitais, & Kim (1993)
- Constrained boundaries within the unified group sequential design family of Kittleson & Emerson (1999)
- Stochastic curtailment

Analyzing and Interpreting Your Results

- Exact p-values
- Exact confidence intervals
- Point estimates adjusted for stopping rules: bias adjusted mean (Whitehead, 1983), median unbiased estimates, UMVUE
- Bayesian posterior inferences (normal prior)
- Inference based on analysis time ordering Tsiatis, Rosner & Tritchler, 1985) and sample mean ordering (Emerson & Fleming, 1990)

System Requirements

S+SeqTrial requires the S-PLUS data analysis package version 2000 or later for operation.

Windows System Requirements

- Pentium processor with 96 MB of memory
- Microsoft Windows NT, ME, 95, 98, 2000.

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