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

S-PLUS®

# S+SeqTrial User's Manual

*February 2000*

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

MathSoft
DATA ANALYSIS PRODUCTS DIVISION

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# OVERVIEW

Welcome to the *S+SEQTRIAL User's Manual*.

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.

A disadvantage of all fixed sample designs is that you always use the same number of subjects regardless of whether the true treatment effect is very beneficial, marginal, or actually harmful relative to the placebo. To address this problem, it is increasingly common to introduce interim analyses in order to ensure patient safety and efficient use of resources.

In a sequential design, data are monitored throughout collection, and a decision to stop a trial can be made before all of the data are accrued. In classical sequential studies, a test 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 basic aspects of fixed sample design–specification of size, power, and sample size–are all present in group sequential design. The difference is that with group sequential tests, sample size is no longer a single fixed number. Instead, the design focus for group sequential tests is selecting a *stopping rule* defining the outcomes that would lead to early termination of the study, along with an appropriate schedule for interim analyses. In this way, the average number of subjects exposed to inferior treatments can be decreased, and the ethical and efficiency considerations of clinical testing are better addressed.

## An Example

Let's look at an example. This manual teaches you how to use S+SEQTRIAL to design, analyze, and interpret a clinical trial like this one.

In a Phase III clinical trial to confirm the benefit of a new drug for the treatment of acute myelogenous leukemia, patients from the Memorial Sloan Kettering Cancer Center were randomly assigned with equal probability to receive either the new treatment (idarubicin) or the standard treatment (daunorubicin). The primary study objective was to demonstrate a difference in the rate of complete remission between the new and standard treatment.

A group sequential design was used for this trial with two interim analyses: one analysis after accruing 45 patients in each treatment arm, and a second analysis after accruing 65 patients. The maximal sample size for the trial was 90 patients in each treatment arm. The left panel of Figure 1 plots the stopping rules for this group sequential design. The design stopped at either of the two interim analyses if the new drug showed superiority or inferiority relative to the existing treatment. Otherwise, it concluded at the final analysis with a decision for superiority of the new treatment, inferiority of the new treatment, or an inability to declare that either treatment is better than the other (which might have been interpretable as approximate equivalence between the two treatments, depending on the minimal difference that was judged clinically important to detect).

For comparison, the right panel shows the fixed sample test with equivalent size and power as the group sequential test.The fixed sample test requires approximately 88 patients per arm, rather than the 90 patients per arm that would be accrued if the group sequential trial continued to the final analysis.

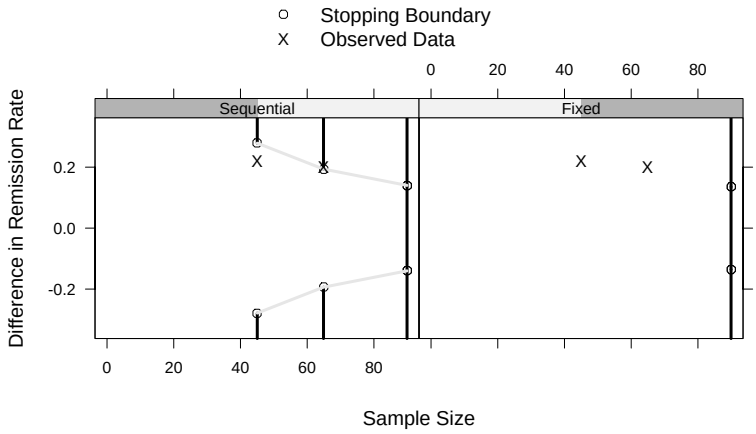


**Figure 1:** *The stopping rules for a group sequential test to demonstrate a difference in the rate of complete remission between a new and standard treatment for acute myelogenous leukemia.*

When the design phase was completed, the trial was begun. At the first analysis, 78% of the patients receiving idarubicin had complete remission as compared with 56% of the patients receiving daunorubicin. The difference in rates, 22%, was not statistically large enough to declare idarubicin better and the trial was continued. At the second analysis, patients receiving idarubicin still had a remission rate of 78% while those receiving daunorubicin had a rate of 58%. A difference in remission rates of 20% was statistically significant at the second analysis and the trial was stopped.

Figure 2 shows the average sample number (ASN) and power curves for both the group sequential test and the fixed sample test with equivalent size and power. The fixed sample test, which has a single analysis after accruing 90 patients in each treatment arm, would have taken considerably longer to complete.

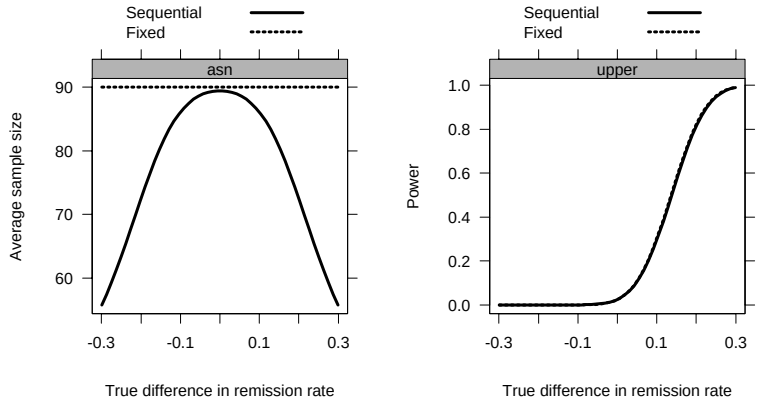


**Figure 2:** *Left plot: the average sample number (ASN) for the group sequential design is substantially smaller than for the equivalent fixed sample test. Right plot: the power curves for the group sequential test and the fixed sample test are visually indistinguishable.*

On average, group sequential designs require fewer subjects than equivalent fixed sample tests. For example, in the trial for treatment of myelogenous leukemia, the ASN for the group sequential test is potentially much lower than for the fixed sample test for (see Figure 2). This increase in efficiency comes essentially without cost: the maximum sample size for the group sequential test is the same as for the fixed sample test and the power curves are virtually identical.

## The Value of S+SEQTRIAL

The difficulty introduced by interim analyses is that you need special methods and software. It is not appropriate to repeatedly apply a fixed sample test; doing so causes an elevation of the Type I statistical error. The sampling density for the test statistic is highly non-Gaussian due to the sequential nature of the test. (See Figure 3 for a typical density.) To adjust the stopping rules so that the test has the desired Type I statistical error, and to compute standard quantities such as power curves and confidence intervals, special software is needed to numerically integrate over such densities. S+SEQTRIAL performs these functions for you.

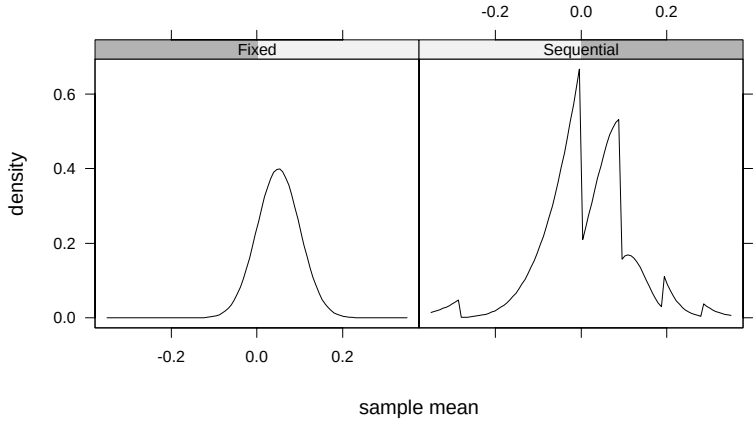


**Figure 3:** *A typical sampling density for the test statistic for a fixed sample test (left) and group sequential test (right). The density for the group sequential test is highly non-Gaussian with discontinuities associated with the stopping boundaries.*

Software is also needed for selecting and evaluating the most appropriate group sequential design. In comparison to fixed sample designs, group sequential tests offer much greater flexibility in the design of a clinical trial. The design parameters include not only power and sample size, but also:

- The number and timing of the analyses;
- The efficiency of the design;
- The criteria for early stopping (evidence against the null hypothesis, the alternative hypothesis, or both);
- The relative ease or conservatism with which a study will be terminated at the earliest analysis versus later analyses.

S+SEQTRIAL helps you to select the best design.

Note that S+SEQTRIAL assumes that the treatment response is evaluated using a test statistic that is approximately normally distributed (for a fixed sample size), and that the increments of

information accrued between successive analyses can be reasonably regarded as independent. The vast majority of clinical trials are based on such statistical tests.

# S+SEQTRIAL FEATURES

S+SEQTRIAL addresses all facets of the conduct of clinical trials: from design to monitoring to analysis. Here are some of the main features of this product.

## A Complete Software Environment

S+SEQTRIAL offers a complete computing environment for applying group sequential methods, including:

- 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 (Windows version only);
- 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;
- Publication quality graphics based on the powerful Trellis Graphics system (Cleveland, 1993; Becker & Cleveland, 1996).

## Stopping Rule Computation

S+SEQTRIAL offers a variety of techniques for computing stopping rules, including:

- 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, Tsiatis, & 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

S+SEQTRIAL includes a variety of techniques for evaluating designs, including:

- 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).

## Monitoring Clinical Trials

S+SEQTRIAL offers a variety of techniques for monitoring trials, including:

- The exact error spending approach of Lan & DeMets (1989) and Pampallona, Tsitais, & Kim (1993);

- Constrained boundaries within the unified group sequential design family of Kittelson & Emerson (1999);
- Stochastic curtailment.

## Analyzing and Interpreting Your Results

Finally, S+SEQTRIAL includes a variety of techniques for analyzing and interpreting your results, including:

- Inference based on analysis time ordering (Tsiatis, Rosner & Mehta, 1984) and sample mean ordering (Emerson & Fleming, 1990);
- Exact *p*-values;
- Exact confidence intervals;
- Point estimates adjusted for stopping rules: bias adjusted mean (Whitehead, 1986), median unbiased estimates, UMVUE;
- Bayesian posterior inferences (normal prior).

# BACKGROUND READING

For users familiar with S-PLUS, this manual contains all the information most users need to begin making productive use of S+SEQTRIAL. Users who are *not* familiar with S-PLUS, should read their *S-PLUS User's Manual*, which provides complete procedures for basic S-PLUS operations, including graphics manipulation, customization, and data input and output.

Other useful information can be found in the *S-PLUS Guide to Statistics*. This manual describes how to analyze data using a variety of statistical and mathematical techniques, including classical statistical inference, time series analysis, linear regression, ANOVA models, generalized linear and generalized additive models, loess models, nonlinear regression, and regression and classification trees.

For references in the field of group sequential statistics, see the Bibliography at the end of this manual. See especially the excellent books by Whitehead (1997) and Jennison & Turnbull (1999).

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