

## Today's presenter



**Alex Dmitrienko**, Ph.D., is Principal Research Scientist at Eli Lilly and Company. He is the coauthor of “Analysis of Clinical Trials Using SAS: A Practical Guide” and has published numerous papers. Alex is actively involved with the Business Intelligence SAS Users Group and the Pharmaceutical Industry SAS Users Group (PharmaSUG), and he won the American Statistical Association's 2005 Excellence in Continuing Education award for his co-presented course on clinical trials. He's currently finishing up a new book titled “Pharmaceutical Statistics Using SAS” that is scheduled for release in October, 2006.

SAS Press webinar

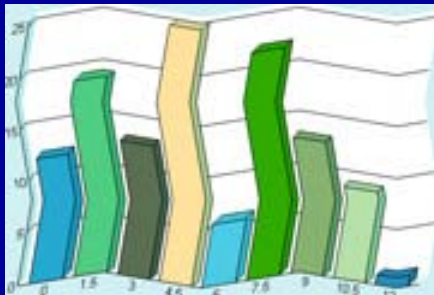
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# Using SAS Software in the Design of Clinical Trials

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Eli Lilly and Company, Indianapolis, IN

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# Outline



Clinical trial challenges

SAS tools used in the design of clinical trials

Example: Flexible trial designs (group sequential designs)

- Standard SAS tools (macros)
- SAS Enterprise Guide modules

Discussion

# Clinical trials challenges

## Clinical trials in 21st century

- 10,000 clinical trials conducted annually
- Increased complexity of trial designs
- Demand to compare multiple competing designs to optimize the information/sample size ratio

## Tools to facilitate/automate trial designs

- Basic tools to compute the number of patients in traditional designs
- Need for advanced tools for designing flexible clinical trials

# SAS tools for traditional designs

## Custom SAS macros

- UnifyPow macro developed by Ralph O'Brien supports a wide variety of designs
- 135 pages of SAS code

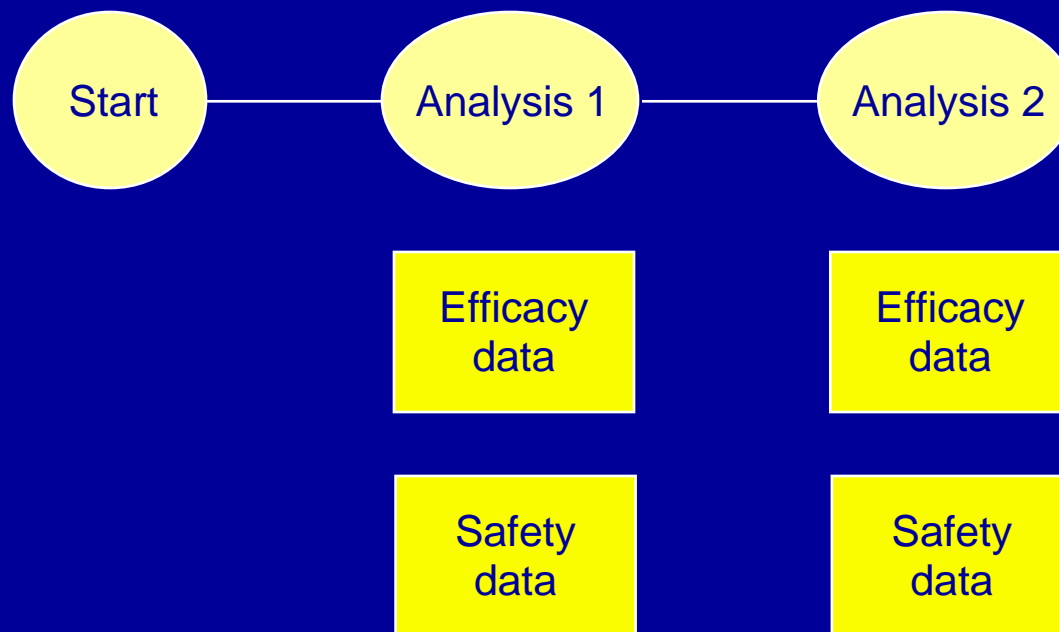
## Built-in SAS tools (SAS Release 9.1.3)

- PROC POWER supports sample size analysis for basic designs
- PROC GLMPOWER handles sample size calculations for linear models (similar to PROC GLM)
- Web-based interface

# Flexible designs

## Group sequential designs

- Safety and efficacy profile of the experimental drug are periodically examined



# Flexible designs

## Ethical requirements and financial considerations

- Ensure that patients are not exposed to harmful therapies
- Make optimal use of research and development dollars

## Flexible decision rule

- Early stopping when the experimental drug is shown to be superior or inferior to the control

# SAS tools for flexible designs

## Commercially available software packages

- Several software packages on the market
- Expensive, cannot be customized
- Do not always have a good graphical user interface

## Custom SAS macros

- Introduced in Chapter 4 of *Analysis of Clinical Trials Using SAS: A Practical Guide*
- Support most popular group sequential designs
- Available at <http://ftp.sas.com/samples/A59390>

# SAS tools for flexible designs

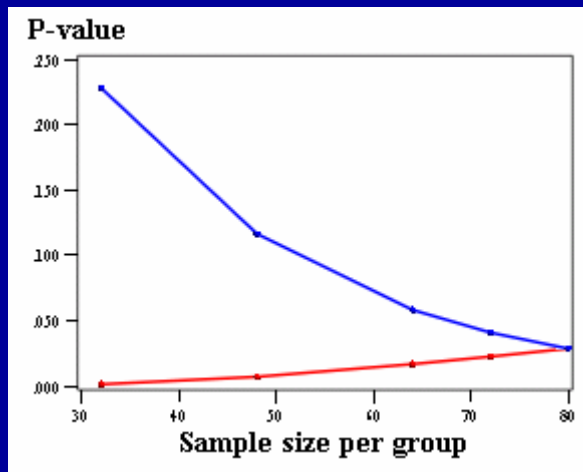
## SAS Enterprise Guide

- A new SAS product
- Four major releases (Version 4.1 in March 2006)
- Supports custom modules with a graphical user interface

## Enterprise Guide module

- Design of group sequential trials
- Available at <http://bisug.org/bix/pharm.html>
- Business Intelligence Exchange maintained by Business Intelligence SAS Users Group (BISUG)

# Clinical trial example



Trial in patients with clinical depression

- A single dose of a new drug versus placebo

Clinical trial with two interim analyses and a final analysis

- Interim looks after 50 and 75 percent of the patients complete the study

# Custom SAS macro

## EffDesign macro

- Computes group sequential designs
- Tabular and graphical summaries of trial designs

## Pros

- Matches important features of commercially available software

## Cons

- Learning curve

# Custom SAS macro

## EffDesign macro call

- %EffDesign(  
fraction=DepTrial,  
effsize=0.375,  
power=0.9,  
alpha=0.025,  
rho=0,  
boundary=OFBoundary,  
sizepower=OFPower);

Powerful macro but requires training

# Enterprise Guide modules

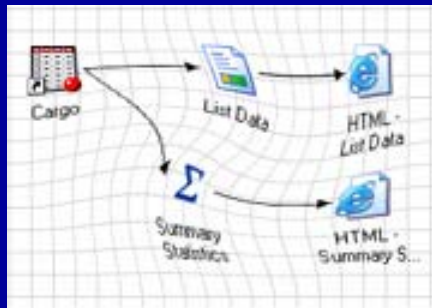
## Enterprise Guide modules vs. SAS macros

- EG modules input certain parameters
- Generate SAS code
- Create output or data sets

## Similarities end

- EG modules are a lot more fun to work with
- Three main reasons to use custom EG modules

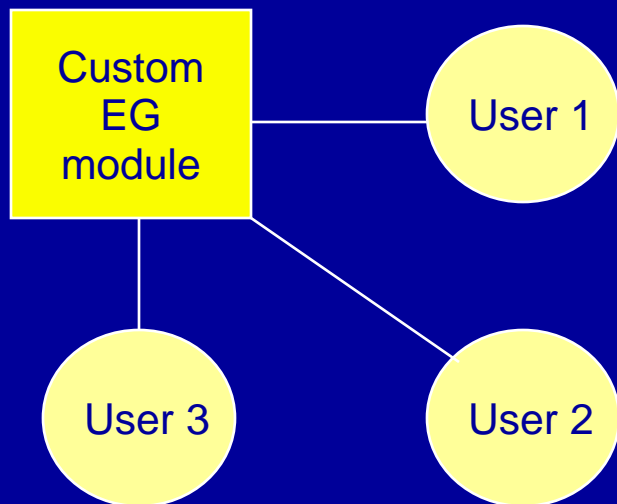
# Benefits of custom EG modules



## EG modules

- “Intelligent” and user-friendly
- Virtually eliminate the learning curve
- Accelerate the design and analysis of clinical trials

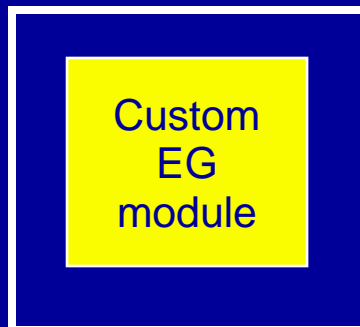
# Benefits of custom EG modules



## EG modules

- Easy to distribute and upgrade
- Can replace quite a few expensive commercial software packages
- The custom module for designing group sequential clinical trials is a good example

# Benefits of custom EG modules



A custom module  
is a black box

EG modules are similar to  
SAS macros

- Same level of validation

EG modules are tamper-proof

- No revalidation work once they  
have been distributed to users

# Custom EG module

Screen 1 (input parameters)

Screen 2 (input parameters)

Generate  
SAS code

Submit the code to SAS

Retrieve and display output

## Wizard-type interface

- Similar to wizards in Microsoft Office programs

## Custom module is a wizard

- Uses an interview format to generate SAS code
- Submits the code to SAS System
- Retrieves output
- Displays output in Enterprise Guide

# Demonstration



## Welcome screen

- A brief summary of features supported by the module

# Demonstration

The screenshot shows a dialog box titled "Design of group sequential trials" with a yellow header and footer. The main area is white. At the top, a yellow banner contains the text "Step 1: Type I error rate and power" in red. Below this, there are two columns. The left column is titled "Type I error rate" and contains a text input field with "0.025". Below the field is the text: "Specify the overall one-sided Type I error rate (0 < Type I error rate < 0.5)." and a note: "Note: To specify a two-sided Type I error rate of 0.05, enter 0.025." The right column is titled "Power" and contains a text input field with "0.8". Below the field is the text: "Specify the power of the trial (0.5 < Power < 1)." At the bottom of the dialog, there are three buttons: "Cancel", "< Back", and "Next >".

Type I error rate	Power
0.025	0.8

Specify the overall one-sided Type I error rate (0 < Type I error rate < 0.5).  
Note: To specify a two-sided Type I error rate of 0.05, enter 0.025.

Specify the power of the trial (0.5 < Power < 1).

Cancel      < Back      Next >

## Step 1

- User specifies parameters of the group sequential design

# Demonstration

**Step 4: Stopping boundary**

**Trial objective**

Efficacy/futility testing

Stop the trial early if the treatment effect is large (efficacy) or very small (futility).

**Shape of stopping boundary**

Upper boundary shape parameter  
0

Lower boundary shape parameter  
0.5

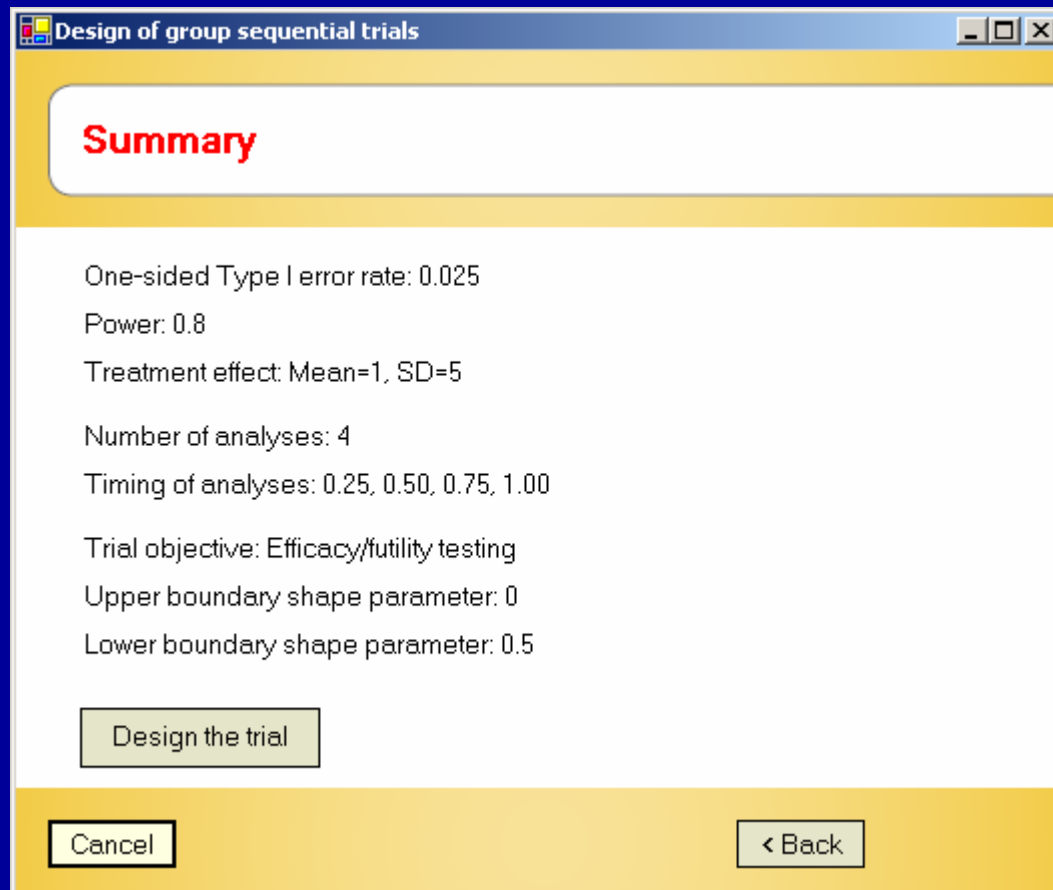
The shape parameter ranges between 0 (O'Brien-Fleming boundary) and 0.5 (Pocock boundary). The smaller the shape parameter, the lower the likelihood of early stopping.

Cancel      < Back      Next >

## Step 4

- User specifies objectives of the trial
- Module provides a detailed description of available options

# Demonstration

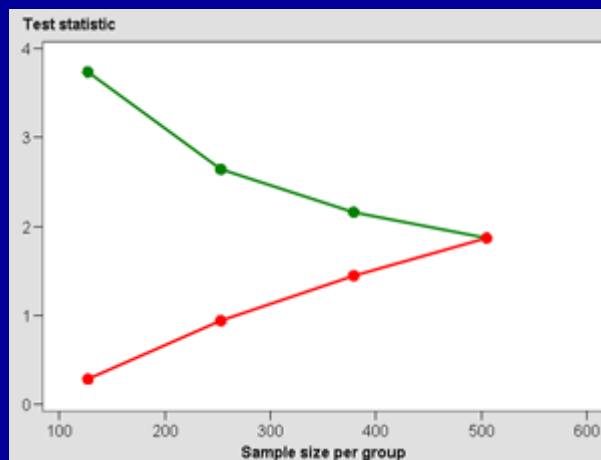


## Summary

- A brief summary of features supported by the module

# Demonstration

Summary	Value
One-sided Type I error probability	0.025
Power	0.8
True effect size	0.2
Number of analyses	4
Fractions of total sample size	0.25, 0.50, 0.75, 1.00
Upper boundary shape parameter	0
Lower boundary shape parameter	0.5
Maximum sample size per group	505
Average sample size per group under H0	198
Average sample size per group under H1	319
Fixed sample size per group	393



## Output

- Module produces tabular and graphical output (HTML, RTF or PDF format)
- Summary of operating characteristics of the group sequential trial design

# Summary

## SAS tools in the design of clinical trials

- Powerful tools for design and analysis of clinical trials

## Standard SAS tools (macros)

- Open source software that relies on the analytical power of SAS System

## SAS Enterprise Guide modules

- Help eliminate learning curve users face with complex SAS macros
- More difficult to develop
- Custom module for design of group sequential trials available at <http://bisug.org/bix/pharm.html>

# Contact Information

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## The SAS Press Webinar Series – Spring 2006



Michael Raithel—February 21

Programmatically Measure SAS Application Performance on any Platform with the New LOGPARSE SAS Macro



Jack Shostak—March 21

Statistical Programming in the Pharmaceutical Industry: Moving Forward, Confronting Challenges, and Embracing Opportunities



Alex Dmitrienko—May 11

Using SAS Software in the Design of Clinical Trials



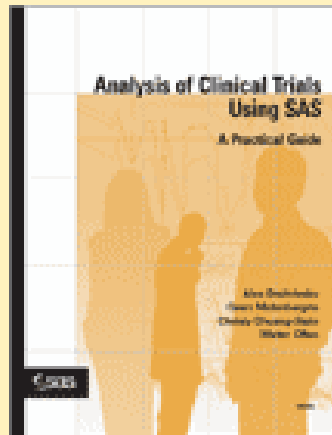
Kirk Lafler—May 25

Tips and Techniques for Producing Quick Results with PROC SQL

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- **PharmaSUG:** May 21 - 24, 2006 Bonita Springs, FL
  - **JMP:** June 20-21, 2006 Cary, NC
    - **JSM/ASA:** August 5 - 10, 2006 Seattle  
Alex is teaching a full day course on *Analysis of Clinical Trials Using SAS: A Practical Guide* along with the coauthors of the book. Preview copies of his forthcoming book "Pharmaceutical Statistics Using SAS" will be available for viewing at PharmaSUG and JSM, as well as additional conferences.
  - **SIG/KDD:** August 20 - 23, 2006 Philadelphia
  - **NESUG:** September 17 - 20, 2006 Philadelphia
  - **WUSS:** September 27 - 29, 2006 Irvine, CA
  - **SESUG:** October 8 - 10, 2006 Atlanta
  - **MWSUG:** October 22 - 24, 2006 Dearborn, MI
  - **M2006:** October 23-24, 2006 Las Vegas

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