NEW AGILE CLINICAL TRIALS SUCH AS ADAPTIVE DESIGNS AND
THE USE OF THE SAS LIFE SCIENCE ANALYTICAL FRAMEWORK

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SAS HEALTH AND LIFE SCIENCES GLOBAL PRACTICE
• Innovation and greater **efficiency in clinical trials** essential. Too many drugs still ‘fail late’ in the development process
• Industry striving to reduce **cost** of the drug development process
  • Costs of getting a drug to market have been continuing to rise
  • Major drugs coming off patent
• Regulatory drive for **innovation** in drug development
  • 2004 FDA Critical Path Paper
  • 2006 Critical Path Opportunities List includes Clinical Trials Optimization
  • 2007 EMEA position paper on adaptive trials
  • 2010 FDA Guidance on adaptive trials
• Technology advances **proven** in other industries supporting
  • Modeling and simulation
  • Decision support using real time data
  • Signal detection
OPTIMIZING PHARMACEUTICAL PRODUCT DEVELOPMENT

Portfolio Optimization
- Which products to develop
- Timing of marketing approvals

Clinical Development Program Optimization
- Trials needed for product submission
- Target markets

Clinical Trial Optimization
- Design
- Process/Execution
THE UNIVERSE OF CLINICAL TRIAL OPTIMIZATION

Clinical Trial Optimization

- Site Auditing QA/Regulators
- Site Monitoring
- Resource Mgmt
- Trial Performance Mgmt
- Clinical Supply Mgmt Forecasting
- Patient Recruitment & Retention
- Site Selection
- Trial Design
- Modeling Simulation
- Analysis & Reporting
“There is great interest in the possibility that clinical trials can be designed with adaptive features (i.e., changes in design or analyses guided by examination of the accumulated data at an interim point in the trial) that may make the studies more efficient (e.g., shorter duration, fewer patients), and more likely to demonstrate an effect of the drug if one exists, or more informative (e.g., by providing broader dose-response information).”
WHY CONSIDER AN ADAPTIVE CLINICAL TRIAL? (1/2)

- Adaptive design approaches can lead to a study that:
  - **Increases the likelihood of success** on the study objective
  - Yields improved understanding of the treatment’s effect (dose response, end-points, subgroup effects)
  - **More efficiently** provides the same information as a conventional design (e.g., futility)
  - Offers **more ethical treatment** of patients (e.g., response adaptive randomization)
  - Increases the likelihood of taking the right dose into phase III (e.g., model-based adaptive dose finding)
  - Delivers **faster** product registration (e.g., seamless phase 2/3)
WHY CONSIDER AN ADAPTIVE CLINICAL TRIAL? (2/2)

• Adaptive clinical trials are not a substitute for poor planning and will not ensure the success of a treatment with marginal efficacy
• Tufts CSDD estimates that early study terminations due to futility and sample size reestimation could save sponsor organizations between $100 million and $200 million annually in aggregate costs
  • direct and indirect costs depending on portfolio size and development cycle time savings
Trial simulations performed prior to a study can help evaluate the design options and the clinical scenarios that might take place when the study is actually conducted.

Simulations can be an important planning tool in assessing the statistical properties of a trial design and the inferential statistics used in the data analysis.

Lots of Options

- Quantitative decision criteria (criteria used to select design)
- Study information (e.g. schedules, treatment arms, sample size, etc.)
- Virtual Patient response models (e.g. PD models incorporating drug-disease models, statistical models incorporating dose response and longitudinal models)
- Trial Execution Models (e.g. dropout/Enrolment rate, compliance)
- Trial design model (patient allocation rules, stopping rules, data sampling rules)
- Data Analysis models (used at trial completion)
- Trial Performance Metrics
SAS FOR ACT

• SAS for ACT helps clinical teams optimize trial design
  • Provides a suite of programs that allow most common phase I and phase II designs to be
    • Defined
    • Simulated
  • Incorporates leading edge trial design innovations as options
    • Dose response modeling
    • Bayesian analysis
    • Longitudinal modeling
    • Response-adaptive features
  • Simulation results presented for comparison of alternative designs
SAS LIFE SCIENCE ANALYTICS FRAMEWORK
KEY FACTS (1/3)

- Managing, analyzing, reporting, and reviewing (clinical) research information in the same analytical environment

  Repository provides seamless integration with the SAS program development (authoring environment) and execution environment, along with workflow capabilities

  -- NEW Authoring Environment compared to SAS DRUG DEVELOPMENT (SDD)

  -- NEW Business Process Model and Notation (BPMN) 2.0 standard support compared to SAS DRUG DEVELOPMENT (SDD)

- Cloud based (Private Cloud @ SAS)

  Provides more flexibility, lower costs, greater scalability, ease of use and, if done correctly, increased security and disaster recovery

  IT at customer end seen as an 'Innovator' supporting the rest of the company to achieve its goals
SAS LIFE SCIENCE ANALYTICS FRAMEWORK
KEY FACTS (2/3)

- **Collaboration & Accessibility**
  - internally and externally (geographically remote) i.e. sponsors, development partners, contract research organizations (CRO), as well as compliance and regulatory stakeholders
  - direct access to research content, clearly organized and searchable

- **Configurable User Interface**
  - Highly flexible (configurable) permission model → privileges & permissions

- **High-performance (Remote) Application Programming Interface** (extend & automate)
  - Java API and SAS Macro API

- **Complete audit history and robust version control system managing change history of all files**

- **Job concept** (reproducibility) and **Manifest file** (transparency / traceability)
SAS LIFE SCIENCE ANALYTICS FRAMEWORK
KEY FACTS (3/3)

- **Standards metadata management** (driving automation)  -- *NEW compared to SAS DRUG DEVELOPMENT (SDD)*
  
  Standard (Global) Level → Data Standards
  Study Level → Studies

- **Support Visual Analytics** (integration)  -- *NEW compared to SAS DRUG DEVELOPMENT (SDD)*

- **Expanding Suite of Extensions**
  
  E.g. ‘Feeds’ to remote locations (via file share or SFTP)
  ‘Pulls’ from remote locations (example: Lab; IxR; … vendors)
  ‘Templates’ to automate creation of folder structure within repository incl. administration
END-TO-END FLOW: PRIMARY RESEARCH

STANDARDS MANAGEMENT – STUDY METADATA – DATA PROCESSING – REVIEW – ANALYSIS

1. Global Standards
   - IMPORT eSHARE CDISC STANDARDS
   - CREATE CUSTOMER STANDARDS

2. Protocol
   - DEFINE STUDY LEVEL METADATA
   - CREATE SUBMISSION READY SDTM DEFINE.XML
   - SHARE WITH INTERNAL & EXTERNAL STAKEHOLDERS

3. EDC Data Extraction
   - (Life Science Analytics Framework Extension/App = available today)

4. SDTM Transformation
   - (Life Science Analytics Framework Extension/App = under development - early phase)

5. Automated + Manual Review Activities
   - (Life Science Analytics Framework Programs/Jobs + SAS® Visual Analytics + Pinnacle 21 (~Open CDISC) + Jreview; Tibco Spotfire, Oracle TMS, ...)
   - Cross-Functional Review Tracking
     - (Life Science Analytics Framework Extension/App = under development - testing phase)

6. Analysis Activities
   - ANALYSIS PROGRAMS-JOBS
     - * CREATION, QC & USAGE (INCL. VERSION CONTROL)
       - * SIGN-OFF
       - * AUTOMATION THROUGH WORKFLOW
         - * RUNNING ‘R’ CODE THROUGH PROC IML
   - VISUALIZATIONS
     - (SAS® Visual Analytics, Tibco Spotfire, ...)
   - ADAPTIVE DESIGN AUTOMATION
     - (Life Science Analytics Framework Adaptive Design Extension/App = under development – testing phase)

Deliverables (Internal sharing of SDTM data after Structure ‘automated’ verification)
LEVERAGING A CENTRALIZED DATA HUB

SAS® for Adaptive Clinical Trials

SDD/LSAF

RBM

Site Selection / Patient Recruitment

Safety Surveillance

Patient Journey

IoT

Text Analytics

RWE

SAS for ACT
### Adaptive Rules

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<thead>
<tr>
<th>ID</th>
<th>Name</th>
<th>Description</th>
<th>Status</th>
<th>Last Run</th>
<th>Met</th>
<th>Schedule</th>
<th>Paths</th>
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<td>30 Patients</td>
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<td>Active</td>
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<td>03-MAY-16 22:29:08 EDT</td>
<td>02:00</td>
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<td></td>
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<tr>
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<td>Interim Safety Run</td>
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<td>Active</td>
<td>22-APR-16 10:02:42 EDT</td>
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<td>Job Results Folder: /SAS/0000/123/output</td>
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Edit Adaptive Rule

History
ID: 3
Name: Interim Safety Run
Description: Run safety analysis at 30 patients complete
Status: Active
Last Run: 22-APR-10 10:02:42 EDT
Rule Met: (not met yet)
SDD Path (Trigger): SAS0000123\mat\check\start\job
SDD Path (Generate Engine Inputs): SAS0000123\mat\gen\inputs\job
SDD Path (Job Results Folder): SAS0000123\output
Recurring Time of Day (GMT): 04 00

Update  Cancel
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<th>Started</th>
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<td>05-APR-16 12:49:00 EDT</td>
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<td>05-APR-16 12:49:00 EDT</td>
<td>Emerton, Eric [SDEV]</td>
<td>05-APR-16 12:49:00 EDT</td>
</tr>
</tbody>
</table>
Extensions (for Adaptive Trials) - Sub-run starting...

Study: 0000-123

Rule ID: 1
Rule Name: 30 Patients
SDD Trigger Job Path: /SAS/0000/123/files/ACT/rules/30patients/checkstart.job
SDD Job Results Path: /SAS/0000/123/files/ACT/rules/30patients/geninputs.job
SDD Path for Engine Inputs: /SAS/0000/123/files/ACT/rules/30patients/inputs_to_facts

Run ID: 28
Current Status: Engine Input Job Running
Action: Starting engine inputs job

Updating rule’s last run date...
Logging into SDD...
Running job in SDD (and waiting for return)...
Job returned with no errors, the engine inputs can now be reviewed...

NOTE: Study adaptive mode is NOT automatic, the engine run will only be queued from screen after a user of appropriate role approves the inputs to an engine run

Logging out of SDD...

---

SAS® Life Science Analytics Framework Extensions

Current Attached Files:

<table>
<thead>
<tr>
<th>File</th>
<th>Added By</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>execute_batch_336.log</td>
<td>System</td>
<td>03-Mar-16 22:20:21 EDT</td>
<td>started run from status: Engine Input Job Running</td>
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<tr>
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<td>System</td>
<td>03-Mar-16 22:20:21 EDT</td>
<td>started run from status: SDD Check Running</td>
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</table>

Add File:

Back to Run
File:
Choose File: No file chosen

---

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## Add Adaptive Run

Use this option to add runs outside of their existing recurring schedule.

<table>
<thead>
<tr>
<th>Rule:</th>
<th>Add</th>
<th>Cancel</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
SAS IS DEVELOPING AN INTEGRATED OPERATIONAL SOLUTION FOR ADAPTIVE CLINICAL TRIAL DESIGNS

- Integrated solution within clinical data management and biostatistics
- Integrated operationally with EDC, IWRS, supply chain, and other clinical operational systems
- Minimizing complexity for all users by developing UI’s that facilitate decision making
- Good opportunity to drive team integration in pharmaceutical organization and with their stakeholders such as CRO’s, DMC and others
- Provide real time data views and study metrics that facilitate decision making, as foreseen in SAP, minimize time lost and unblinding risks
Six steps of a group sequential design

1. Trial specification
2. Compute boundary values and sample size
3. Collect data according to trial to required sample size
4. Analyze data and compute test statistic
5. Compare test statistic with boundary values (reject, accept, continue)
6. Compute parameter estimates, confidence limits for the parameter, and a p-value for the hypothesis test
SEQUENTIAl
DESIGN AND
ANALYSIS

• Proc SEQDESIGN
  • Design interim analyses for clinical trials
  • Compute
    • Boundary values
    • Maximung and average sample size
    • Stopping probabilities
    • Numbers of events required at each stage (survival data)

• Proc SEQTEST
  • Perform interim analyses for clinical trials
  • Compare the test statistic with the corresponding boundary at each stage
  • Boundary adjustment for information levels
  • Sample space ordering
  • Parameter estimate, p-value, confidence limits at the conclusion of a trial