Secure Interim Analysis Data Access and Automated DMC/DSMB Management with ACES®

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Introductions: Today’s Speakers

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What You Will Learn

• The considerations when forming information paths for DMC/DSMB communications
• Scheduling an interim analysis – when is best?
• How to build firewalls to protect interim data
• What can you do to build regulatory trust?
• How to automate generation of supporting documentation needed for interim analysis
• How is ACES being used today?
Agenda

- Background
- Traditional Process Concerns
- DMC/DSMB Communications
- Planning Interim Analyses
- Where Does ACES® Fit In?
- Actual and Potential Benefits
- Closing Remarks
- Q&A
Over the past 10 years, there has been a significant increase in the use of Data Monitoring Committees.

- Safety monitoring is required
- Role of DMCs is expanding and becoming more complex
- Traditional DMC responsibilities
- Adaptive design clinical trials increase DMC responsibility
- Adaptive design requires a communication plan that allows for trial modifications after interim analyses
Key Roles in Interim Analyses

• Sponsor
• Independent Statistical Center (ISC)
• Data Monitoring Committee (DMC)
  Data Monitoring Safety Board (DSMB)
• Steering Committee
• IVRS
• EDC
• Drug Supply
Traditional Process

Sponsor

1. Create Documents (Protocol, SAP, DMC Charter)
2. Store/Archive Documents
3. Enroll Subjects & Collect Responses
4. Send Response Data to ISC

ISC

- Send Analysis to DMC
- Request additional information

 DM C

- Make Recommendation
- Send Recommendation to Sponsor/Steering Committee

After decision...
1. DMC notified
2. Drug Supply notified
3. IVRS notified

Steering Committee

- Make Decision About Trial
- Perform Analysis and Create Reports
- Create and Test Analysis Programs

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Concerns with Traditional Process

• SOP Training and Enforcement
• Firewall Implementation
• Operational Bias
  – Unblinded Analyses
  – Blind Maintenance
  – Assurances of Limitation
    • Sponsor Involvement
    • Steering Committee Involvement

• Lack of Consistency
  – Process
  – Notifications
  – Snapshots
    • Interim Analyses Data
    • Analysis Programs
    • Output
  – Documentation
    • Who, What, When

• Security
  – Information Access
  – Lack of Auditing
ACES is a secure, web-based platform to help clinical teams implement fixed and adaptive trial designs with interim analyses.

- Workflow Automation
- Secure Firewalls
- Document Storage
- Auditing
- Reporting
- Global Access
Protect Trial Integrity

- Create Secure Firewalls
  - Unique Usernames and Passwords
  - Role Based Security
  - Maintains Study Blind
- Document and Information Storage
  - Centralized
  - Controlled Access
  - Auditable
Reduce Operational Bias

• Automated Analysis
  – Blinded Interim Analysis
• Restrict Access to Blinded Information
  – Limit Sponsor Involvement
• Control Access to Information
  – Centralized Information Portal
Firewalls
Firewalls

Information Portal

Unblinded

Blinded

DMC and ISC

Sponsor and Steering Committee
Building Firewalls and Protecting Data

• “Sponsor exposure to unblinded interim data, through the DMC or otherwise, can present substantial risk to the integrity of the trial.”
• “Unblinded interim data and the results of interim analyses should not be accessible by anyone other than DMC members or the statistician(s) performing these analyses and presenting them to the DMC.”
• “Sponsors should establish written procedures, which may be included in the DMC charter, to ensure the minimization of bias, such as maintaining confidentiality of the interim data.”

ACES satisfies these requirements by enforcing the rules identified in the DMC Charter, and by providing unequivocal evidence of that enforcement.

Source: FDA Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006
"A well-trusted firewall established for trial conduct beyond those established for conventional group sequential trials can help provide assurance that statistical and operational biases have not been introduced."

*FDA Draft Guidance on Adaptive Design (2010)*
Automating Analysis and Reporting

- FDA recommends that the DMC or the group preparing the confidential interim reports to the DMC maintain all meeting records in order to best ensure continued confidentiality of interim data.
- FDA may request copies of these records when the study is completed.
- FDA may also request access to the electronic data sets used for each set of interim analysis.
- FDA recommends that sponsors arrange for archiving such electronic data sets.

ACES satisfies these requirements providing capabilities to automate interim analysis reporting, archive input data sets and output reports, and maintain meeting records.

Source: FDA Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006
Increase Regulatory Trust

- Auditing
- Accountability
- Automatic Snapshots
  - Data
  - Parameters
  - Outputs
  - Decisions
- Real-Time Process Inspections
- Consistency
ACES Process

**Sponsor**
- Create Documents (Protocol, SAP, DMC Charter)
- Store/Archive Documents in ACES

**ISC**
- Send Analysis to DMC in ACES
- Perform Analysis and Create Reports in ACES
- Load final Analysis Programs into ACES
- Create and Test Analysis Programs

**DMC**
- Send Recommendation to Sponsor/Steering Committee
- Make Recommendation

**Steering Committee**
- Make Decision about Trial
- After decision... 1. DMC notified 2. Drug Supply notified 3. IVRS notified

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Benefits of Using ACES

Access
- Centralized
- Web Based
- Internal and External Users

Control
- User Authentication
- Firewalls
- Access Restrictions

Workflow
- User Management
- Trial Design
- Interim Analyses Planning

Documentation
- Trial Documents
- Interim Analyses
- Audited Access

Consistency
- Across Studies
- Process
- Communication

Trust & Confidence
- Transparency
- Evidence
- Reporting
System Integrations

- Statistics Packages
  - SAS
  - R

- Document Management Systems
  - Information Portal
  - Security
  - Audit Trail
  - Automated Analysis
  - Process Tracking (Workflow)
  - Document Storage
  - Interim Snapshots

Document Management Systems

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Future Extensions and Integrations

**Design/Simulation**
- Algorithm
- Parameter Data

**CTMS**
- Trial Data
- Investigator/Site Data
- Planned Metrics

**Dashboards and Analytics**
- Subject Events/Responses
- Enrollment Forecasting
- Drug Supply Forecasting
- Site Monitoring Optimization
- Portfolio Management/NPV

**IVRS/IWRS**
- Randomization Data
- Dynamic Change/Update Treatment Probabilities

**EDC**
- Subject Data
- Response Data

**Drug Supply**
- Warehouse and Site Inventories
- Resupply Thresholds
Actual and Potential Benefits

• Using ACES® for executing trials and performing interim analyses enables
  – Isolation of the unblinded trial data to a secure environment
  – Avoids any question of affecting the trial integrity
• All interim analyses process, data, and decisions are captured for a complete trial history
• Guarantees that no changes were made to critical documents after data was unblinded
  – Statistical Analysis Plan (SAP)
  – DMC Charters
  – Protocol Document
• Generates and securely stores blinded or unblinded reports for review by targeted individuals
  – More secure than e-mail or UPS/FedEx
  – Unequivocal assurance that key users (ISC, DMC) have opened documents
Closing Remarks

• **Operational Bias** is greatly reduced by using secure systems, and by limiting access to unblinded data

• **Trial Integrity** is protected by documenting the conduct, logistics, and operation of the trial through security and audit trails

• **Regulatory Confidence** in the consistent execution of adaptive trials by implementing systems that enforce ‘best practice’ processes
Learn More – Meet Us

**SMi Adaptive Designs in Clinical Development**
Eric speaks on protecting trial integrity, reducing operational bias, and building regulatory confidence when conducting interim analyses

**ICSA Applied Statistics Symposium**
Boston, June 23-26, 2012
Eric’s talk titled, *Optimizing Human Interactions and Information Flow During Interim Analyses*

**ASCO**, Chicago, June 1-5, 2012
Cyrus Mehta, Cytel President

**BIO**, Boston, June 19-21, 2012

**DIA**, Philadelphia, June 24-28, 2012

Exact times & places TBA: [watch cytel.com](http://cytel.com)
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Thank you.
Learn More - References

- [FDA Draft Guidance on Adaptive Design Clinical Trials](source: www.fda.gov)
- [FDA Guidance on Data Monitoring Committees](source: www.fda.gov)
- [EMEA Guideline on Data Monitoring Committees](source: www.emea.europa.eu)
Thank You for Joining Today

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