

# Combining Design and Execution of Adaptive Trials: AML Case Study

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# The VALOR Trial

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- Phase 3 randomized, controlled, double-blind, multinational trial in patients with first relapsed or refractory acute myeloid leukemia (AML)
- Evaluates the efficacy and safety of vosaroxin plus cytarabine versus placebo plus cytarabine

(vosaroxin is a first-in class anticancer quinolone derivative, or AQD, under development by Sunesis Pharmaceuticals, Inc.)



# Part I: Design Considerations

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- Primary endpoint is overall survival (OS)
- Design for 90% power; 5% significance level
- Plan for 24 month enrollment; 30 month trial
- Base Case Scenario
  - 5 vs. 7 month median on Ctrl vs.Trtm (HR=0.71)
  - 375 events and 450 patients @ 19/month
- Alternative Scenario
  - 5 vs. 6.5 month median on Ctrl vs. Trtm (HR=0.77)
  - 617 events and 732 patients @ 31/month
  - Requires larger upfront investment of resources and patients



# Sponsor Favors Staged Commitment of Resources and Patients

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Initial investment in base case  
scenario with commitment to  
invest additional resources  
**if interim results are  
promising**



# Sponsor's Dilemma

| True HR           | Power if designed with base case assumption (HR=0.71) | Power if designed with alternative assumption (HR=0.77) |
|-------------------|---|---|
| 0.71              | 91%   | 99%   |
| 0.74              | 83%   | 97%   |
| 0.77              | 71%   | 90%   |
| Population Needed | 450 patients; 375 events                              | 732 patients; 616 events                                |

- Sponsor conducted robust Phase 2 (N=69), though with inherent limitations of: small sample relative to Phase 3; non-randomized data; US-only conduct
- The true HR is not known but expected to be between 0.71 and 0.77
  - Trial would be underpowered if designed for HR=0.71 but true HR > 0.71
  - Trial would be overpowered if designed for HR=0.77 but true HR < 0.77
- Preferred decision : to invest additional patients, resources, and time on larger study only if warranted, based on interim results, rather than upfront



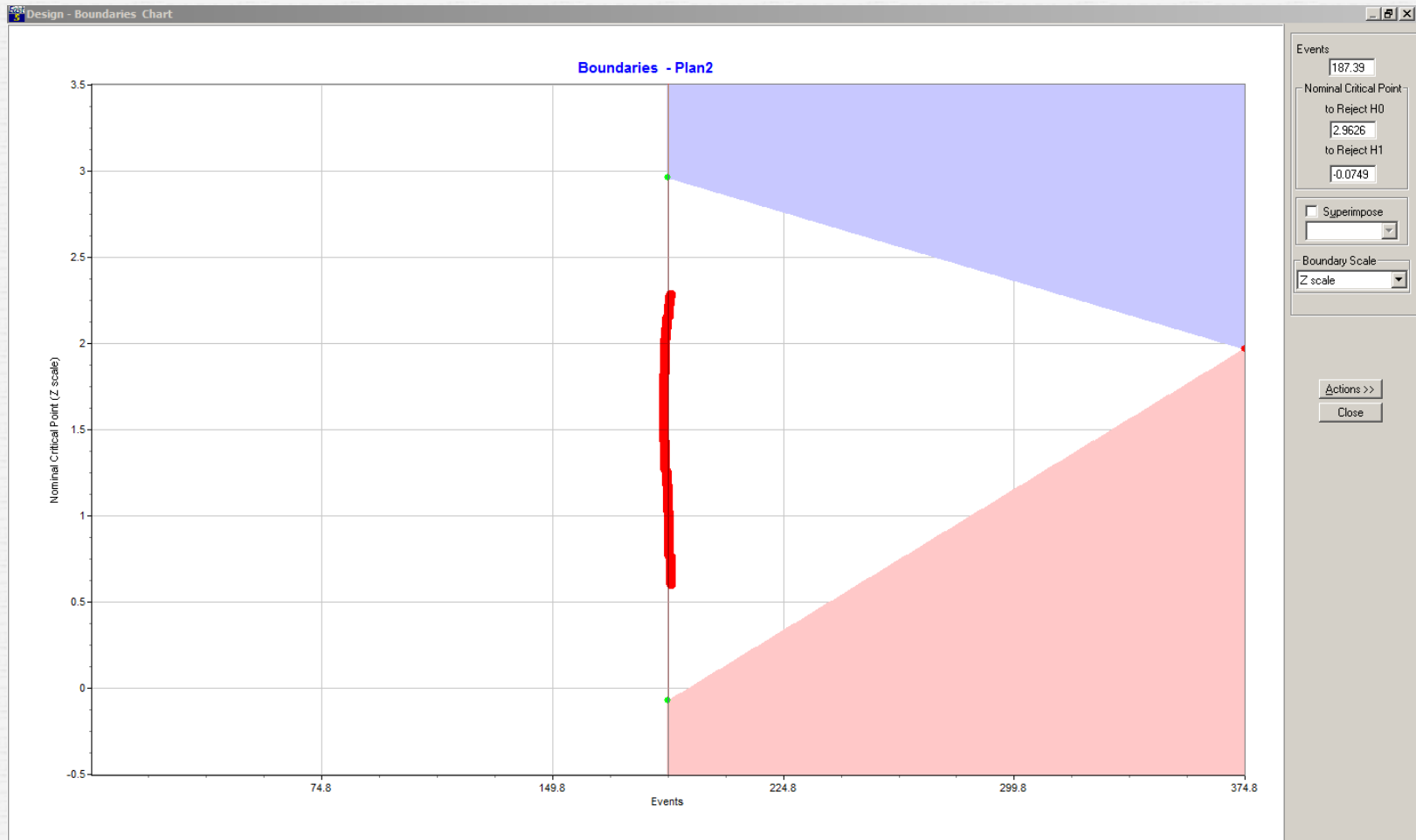
# Adaptive Design Strategy

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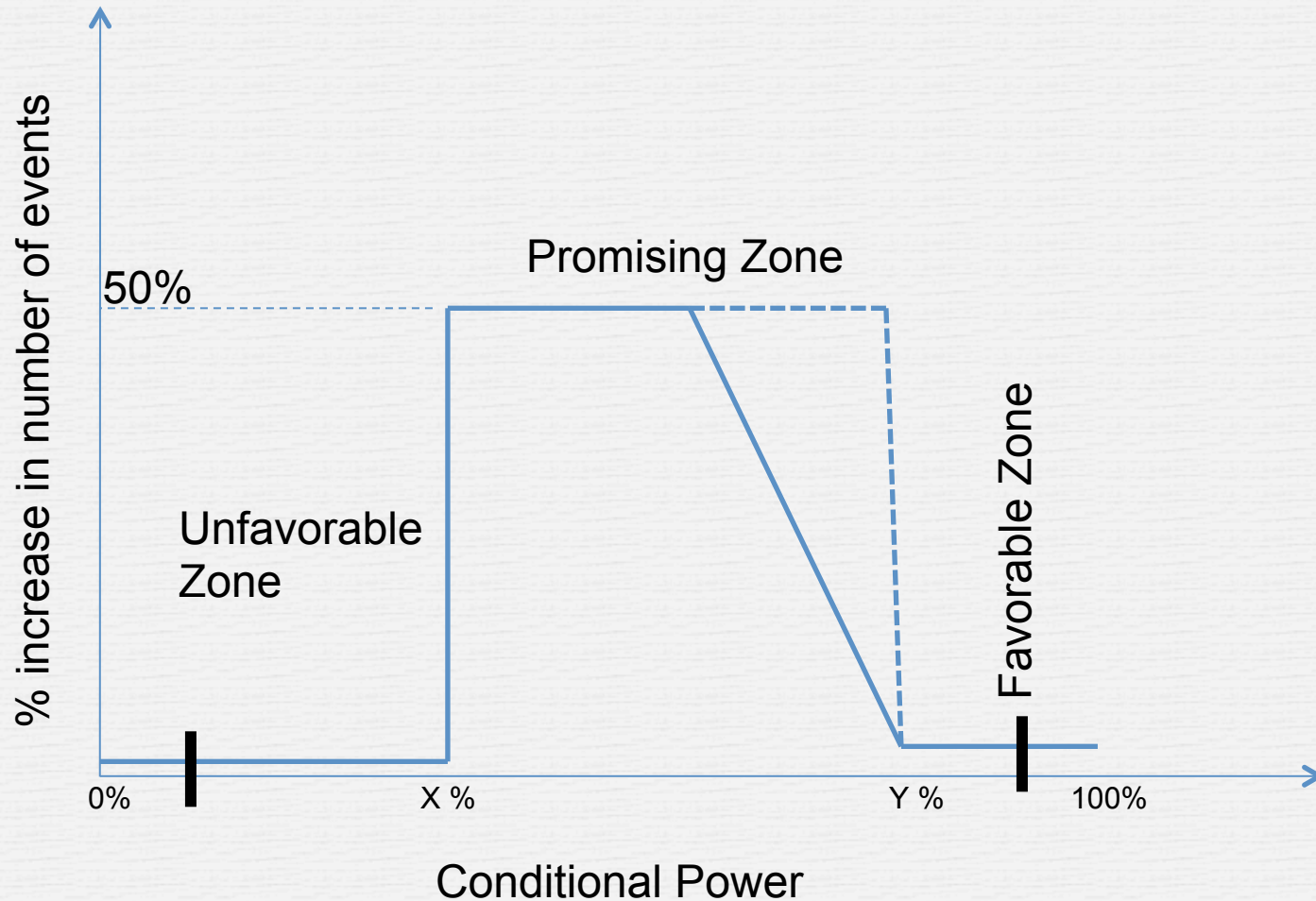
- Base case design (HR=0.71; 375 events; 450 patients)
- One interim analysis after 50% of information
  - Stop early if overwhelming evidence of efficacy
  - Stop early for futility
  - Increase number of events and sample size (by 50%) **if interim results are promising**



# Adaptive Decision Rule: I (Example)



# Adaptive Decision Rule: II (Example)



# Statistical Methodology

Use well established method of combining independent increments from the two stages with pre-specified weights

$$Z_{j,\text{chw}}^* = \frac{\sqrt{w^{(1)}} Z^{*(1)} + \sqrt{w^{(2)}} Z^{*(2)} + \dots + \sqrt{w^{(j)}} Z^{*(j)}}{\sqrt{w^{(1)} + w^{(2)} + \dots + w^{(j)}}}$$

where

$$Z^{*(j)} = \frac{\sqrt{D_j^*} \text{LR}_j - \sqrt{D_{j-1}^*} \text{LR}_{j-1}}{\sqrt{D_j^* - D_{j-1}^*}} \quad \text{and} \quad w^{(j)} = \frac{D^{(j)}}{D_{(K)}}$$

Reference: Lehmacher and Wassmer, 1999; Cui, Hung and Wang, 1999



# Evaluate Properties by Simulation: (Example)

## Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration

Perform Adaptation if Necessary (During Simulations)

| Input Parameters                                  |              |
|---|--------------|
| Adaptation at Look L                              | 1            |
| Max. Events if Adapt (multiplier; total #)        | 1.50 561     |
| Max. # of Subjects if Adapt (multiplier; total #) | 1.50 677     |
| Upper Limit on Study Duration                     | 90.00        |
| Shape Parameter for Re-estimating # of Events     | 0.99         |
| Promising Zone :                                  | Min CP: 0.50 |
|   | Max CP: 0.90 |
| HR Used in CP Computations                        | Estimated HR |
| Accrual Rate After Adaptation                     | No Change    |

| Output for all Trials |                |                  |                  |                    |
|-----------------------|----------------|------------------|------------------|--------------------|
| Show Summary for      |                |                  |                  | Promising          |
| Percentile            | Study Duration | Number of Events | Accrual Duration | Number of Subjects |
| 5%                    | 37.0           | 561              | 35.1             | 677                |
| 25%                   | 37.7           | 561              | 35.6             | 677                |
| 50%                   | 38.3           | 561              | 36.0             | 677                |
| 75%                   | 38.9           | 561              | 36.3             | 677                |
| 95%                   | 39.7           | 561              | 36.8             | 677                |
| Average               | 38.3           | 561              | 36.0             | 677                |

Run Single Step Reset Stop

### Simulation Results by Zone

| Zone                               | Simulations Rejecting H0 |        | Simulations Rejecting H1 |        | Total Simulations |          | Avg. Study Duration | Avg. Number of Events | Avg. Accrual Duration | Avg. Number of Subjects |
|------------------------------------|--------------------------|--------|--------------------------|--------|-------------------|----------|---------------------|-----------------------|-----------------------|-------------------------|
|                                    | Count                    | Row %  | Count                    | Row %  | Count             | Column % |                     |                       |                       |                         |
| + Unfavorable + Futility           | 1394                     | 40.06% | 2086                     | 59.94% | 3480              | 34.80%   | 28.3                | 358                   | 23.4                  | 440                     |
| Promising: $0.500 \leq CP < 0.900$ | 2295                     | 92.43% | 188                      | 7.57%  | 2483              | 24.83%   | 38.3                | 561                   | 36.0                  | 677                     |
| + Favorable + Efficacy             | 3844                     | 95.22% | 193                      | 4.78%  | 4037              | 40.37%   | 25.6                | 317                   | 21.9                  | 412                     |
| All Trials                         | 7533                     | 75.33% | 2467                     | 24.67% | 10000             | 100.00%  | 29.7                | 392                   | 25.9                  | 488                     |



# Benefit of Adaptive Design

| True HR | Base Case Design<br>450 Patients, 375 Events | Adaptive Design<br>675 Patients, 563 Events |
|---------|--|---|
| 0.71    | 91%  | 98%   |
| 0.74    | 83%  | 96%   |
| 0.77    | 71%  | 90%   |
| 0.80    | 58%  | 84%   |

- VALOR's adaptive design gains substantial additional power over non-adaptive IF interim outcome falls in the Promising Zone (~35% chance)



# Part II: Operational Considerations

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- Statistical methodology for controlling type-1 error is well established (Cui, Hung and Wang, 1999, East-SurvAdapt, 2011)
- Logistical and operational issues associated with trial execution are less well established
- We have implemented a web solution for handling the two main issues of concern to regulatory agencies: **operational bias** and **trustworthiness**



# What is Required?

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"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 Guidance on Adaptive Design (2010)*



# Operational Bias and Trustworthiness

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- **Operational Bias**

- Can knowledge that the sample size was increased (or not increased) affect the integrity of the study?

- **Trustworthiness**

- Who saw what data, and when?
- Can a non-invasive audit trail of the entire data handling process be implemented?



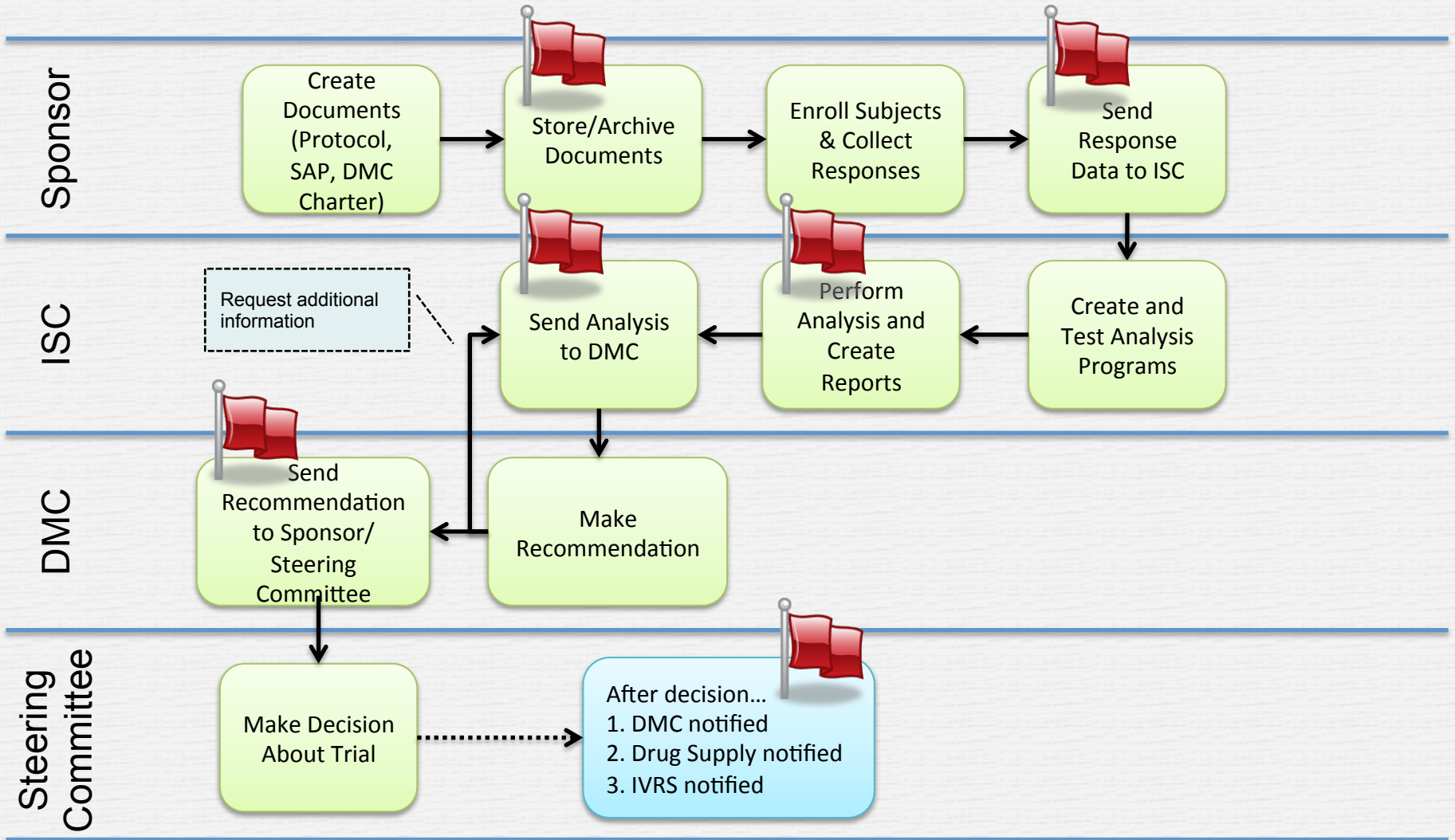
# ACES: Access Control Execution System

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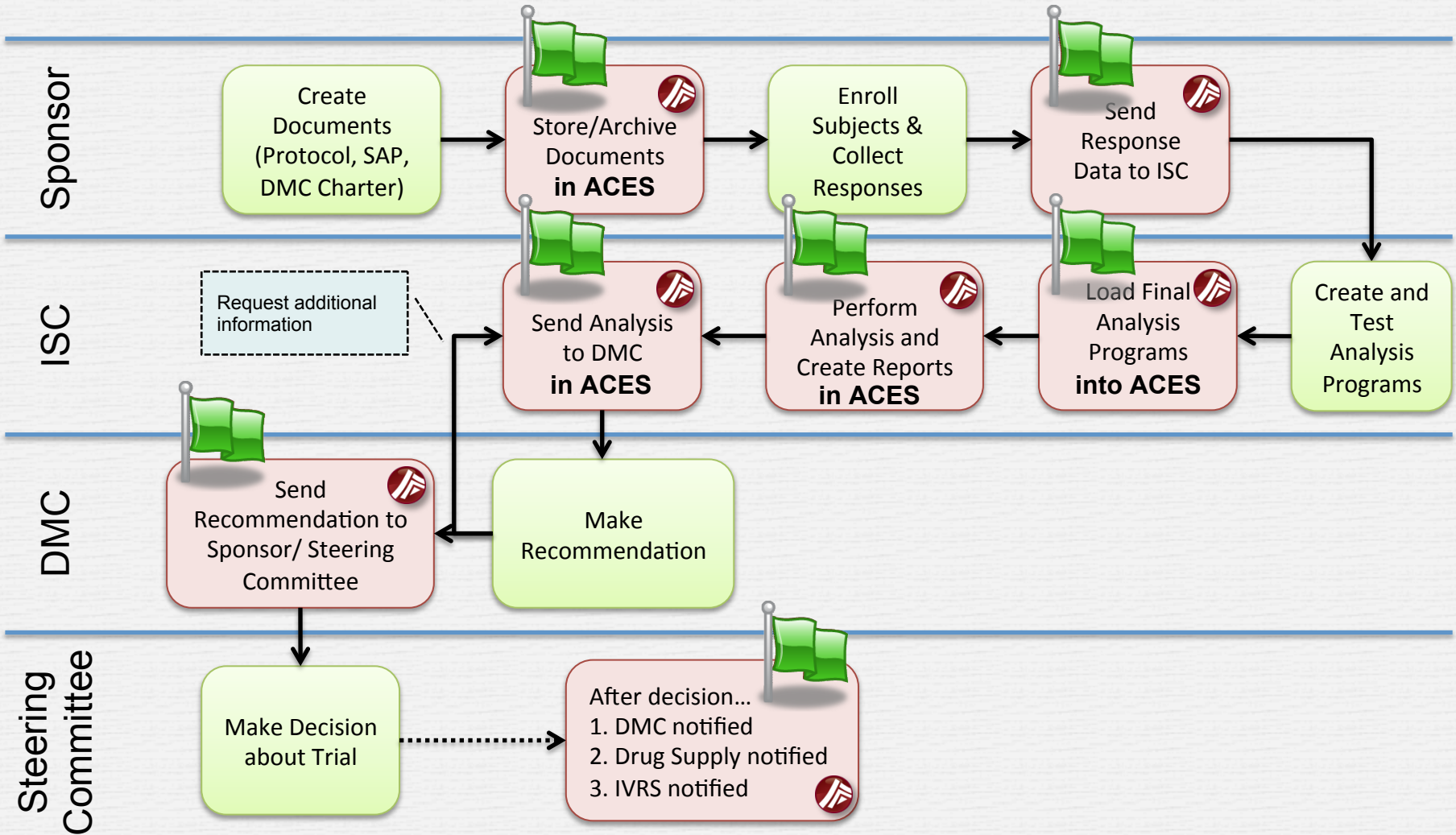
- Web based technology to control flow of information and access to confidential documents
- **Prevents operational bias** by including the actual adaptive algorithm only in restricted appendix to Data Monitoring Committee (DMC) charter and tracking access to this document
- **Establishes trustworthiness** through secure password protected access to documents, execution of algorithms, and audit trail



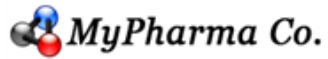
# Traditional Process



# ACES Process



# Sign In



Welcome to ACES. Please enter your User ID and Password to sign in.

Sign In to ACES

User ID:

Password:

[Forgot your password?](#)

By logging into ACES I accept and agree to the following terms. I understand that my very use of ACES authenticates me as the official requestor and user of this ACES account. I understand that access to ACES is restricted to authorized personnel.



# Document Dashboard

The screenshot shows the MyPharma Co. Document Dashboard. At the top left is the MyPharma Co. logo. At the top right is a 'Sign Out' button. Below the logo is a blue navigation bar with 'Document Viewer' and 'Logged In Time: 14-Feb-2011 21:52:00 (UTC) | david.gilmour'. On the left is a vertical menu with 'Dashboard', 'Document Viewer', and 'Change Password'. The main content area has a header with 'Study: ALC-123', 'Current Version: V1.0', 'Study State: Open', and 'ADI Name: Albert'. Below this are 'Last Execution Cycle Run: Active-Interim Analysis-2' and 'Last Execution Cycle Run Date: 11-Feb-2011'. The main area is split into 'Categories' and 'List of Documents'. The 'Categories' section shows a tree view with 'Study Documents' selected, containing 'Protocol Documents', 'DMC Minutes', 'Active-Interim Analysis-1', 'DMC Reports', and 'Active-Interim Analysis-2', 'DMC Reports'. The 'List of Documents' section is a table with 5 columns: Document Name, Category, Description, Uploaded By, and Date Uploaded. It lists four documents: 'DMC Meeting Minutes', 'Study Protocol', 'DMC Charter', and 'SAP Document', each with a 'NEW' badge. The table footer shows 'Displaying items 1 - 4 of 4'.

MyPharma Co. Sign Out

> Document Viewer Logged In Time: 14-Feb-2011 21:52:00 (UTC) | david.gilmour

Dashboard  
Document Viewer  
Change Password

Study: ALC-123 Current Version: V1.0  
Last Execution Cycle Run: Active-Interim Analysis-2 Study State: Open  
Last Execution Cycle Run Date: 11-Feb-2011 ADI Name: Albert

Document Dashboard Import Documents

**Categories**

- Study Documents
  - Protocol Documents
  - DMC Minutes
- Active-Interim Analysis-1
  - DMC Reports
- Active-Interim Analysis-2
  - DMC Reports

**List of Documents**

| Document Name                             | Category           | Description                            | Uploaded By | Date Uploaded        |
|---|--------------------|--|-------------|----------------------|
| <a href="#">DMC Meeting Minutes</a>       | DMC Minutes        | DMC Closed Session Minutes 01-Feb-2011 | David       | 14-Feb-2011 21:50:33 |
| <a href="#">Study Protocol</a> <b>NEW</b> | Protocol Documents | Study Protocol                         | Stephen     | 14-Feb-2011 21:45:41 |
| <a href="#">DMC Charter</a> <b>NEW</b>    | Protocol Documents | DMC Charter                            | Stephen     | 14-Feb-2011 21:45:39 |
| <a href="#">SAP Document</a> <b>NEW</b>   | Protocol Documents | Statistical Analysis Plan              | Stephen     | 14-Feb-2011 21:45:30 |

Displaying items 1 - 4 of 4



# Execution Cycle

Interim Analysis begins...    Responses Generated...    Reports Generated.

Study:  Study Version:  Current Version Status: Active

Execution Cycle Summary    Execute Design Run    Inputs/Outputs    Run Errors    Pending Actions

Execution Cycle Summary Dashboard  Show Test Execution Cycles

| Run Number | Date of Run          | Study Version | Version Status | Execution Status          | Classification        | Inputs / Outputs     | Errors | Pending Actions | Reports              | Randomization Output                    |
|------------|----------------------|---------------|----------------|---------------------------|-----------------------|----------------------|--------|-----------------|----------------------|---|
| 3          | 14-Feb-2011 10:15:16 | V1.0          | Active         | Generating Responses      | Interim Analysis      | <a href="#">View</a> |        |                 |                      |   |
| 2          | 11-Feb-2011 06:46:07 | V1.0          | Active         | Execution Cycle completed | Interim Analysis      | <a href="#">View</a> |        |                 | <a href="#">View</a> | <a href="#">Treatment Probabilities</a> |
| 1          | 10-Feb-2011 05:21:27 | V1.0          | Active         | Execution Cycle completed | Interim Analysis      | <a href="#">View</a> |        |                 | <a href="#">View</a> | <a href="#">Treatment Probabilities</a> |
| 1          | 09-Feb-2011 03:38:33 | V1.0          | Test           | Execution Cycle completed | Test Run On Test Data | <a href="#">View</a> |        |                 | <a href="#">View</a> | <a href="#">Treatment Probabilities</a> |



# Audit Trial: Document Access Log Summary

| <b>Document Access Log Summary: 12</b>     |                    |  |               |
|--|--------------------|--|---------------|
| <b>Document:</b> Alcohol Dependency Report |                    | <b>Created On:</b> 09-Feb-2011 15:39 UTC |               |
| <b>Accessed on</b>                         | <b>Accessed by</b> | <b>Uploaded by</b>                       | <b>Status</b> |
| 09-Feb-2011 15:40 UTC                      | Albert Einstein    | SYSTEM                                   | ACCEPTED      |
| 09-Feb-2011 15:45 UTC                      | David Gilmour      | SYSTEM                                   | ACCEPTED      |
| <b>Document:</b> Alcohol Dependency Report |                    | <b>Created On:</b> 10-Feb-2011 17:22 UTC |               |
| <b>Accessed on</b>                         | <b>Accessed by</b> | <b>Uploaded by</b>                       | <b>Status</b> |
| 10-Feb-2011 17:23 UTC                      | Albert Einstein    | SYSTEM                                   | ACCEPTED      |
| 10-Feb-2011 17:29 UTC                      | David Gilmour      | SYSTEM                                   | ACCEPTED      |
| 11-Feb-2011 18:50 UTC                      | David Gilmour      | SYSTEM                                   | ACCEPTED      |
| <b>Document:</b> Alcohol Dependency Report |                    | <b>Created On:</b> 11-Feb-2011 18:48 UTC |               |
| <b>Accessed on</b>                         | <b>Accessed by</b> | <b>Uploaded by</b>                       | <b>Status</b> |
| 11-Feb-2011 18:48 UTC                      | Albert Einstein    | SYSTEM                                   | ACCEPTED      |
| <b>Document:</b> SAP Document              |                    | <b>Created On:</b> 14-Feb-2011 21:45 UTC |               |
| <b>Accessed on</b>                         | <b>Accessed by</b> | <b>Uploaded by</b>                       | <b>Status</b> |
| 14-Feb-2011 21:45 UTC                      | Stephen Hawking    | Stephen Hawking                          | ACCEPTED      |
| <b>Document:</b> DMC Charter               |                    | <b>Created On:</b> 14-Feb-2011 21:45 UTC |               |
| <b>Accessed on</b>                         | <b>Accessed by</b> | <b>Uploaded by</b>                       | <b>Status</b> |
| 14-Feb-2011 21:45 UTC                      | Stephen Hawking    | Stephen Hawking                          | ACCEPTED      |



# Review: What Problems did ACES Address?

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- **DMC Portal**
  - secure centralized storage of documents
  - customized access for DMC, Independent Statistical Center (ISC), and Sponsor
- **ACES Engine Generates Interim Reports**
  - analysis programs pre-tested and loaded to ACES
  - blinded dataset uploaded to ACES
- **Non-Invasive Audit Trail**
  - who sees what and when is time stamped
  - dataset and analysis program available for review



# Concluding Remarks

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- Adaptive design reduces risk of failing to detect a smaller clinically meaningful effect
- Pragmatic approach; wait to see data before committing additional patients and resources
- Statistical methodology well understood
- Operational challenges and trustworthiness are regulatory concerns that are handled well by the ACES system



# Acknowledgements

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