

## Access Control Execution System (ACES)

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### Abstract

Adaptive trials have gained increasing acceptance both by the industry as well as regulators. There is growing interest towards the usage of adaptive methodology in clinical trials. There are two main challenges in implementing clinical trial, especially adaptive clinical trials. One is scalability, constrained by the sheer manual overhead and the other, maintaining the trial integrity, constrained by manual procedures. These strongly point to the need for an execution-system that can automate the manual efforts and enforce access controls.

In this paper the authors will discuss Cytel's ACES, a web-based system that specifically addresses these needs – for both adaptive and conventional trial. ACES supports different types of trials; provides access and security within a controlled environment; manages the interim analysis workflow; notifies users of new trial activity;; and provides secure access to reports and trial documents. ACES provides an environment for executing the trial with detailed audit tracking, accurately capturing the information flow, data modifications, and user conduct during the trial, i.e., who has done what, and when.

### Introduction

Access Control Execution System (ACES) is a comprehensive and independent execution environment for adaptive trials and conventional trials.

ACES operates as a stand-alone system to configure a trial, perform interim monitoring, and provide auditing of activity, but also has the capability to integrate and communicate with external systems including those of the trial sponsor and CRO organizations. ACES is designed to be independent of the trial being executed and the statistical computation programs used for the interim monitoring.

In this paper the authors will explain the usage of ACES, and how it can satisfy the regulatory and industry needs, as well as delivering gains in resource efficiency and reduction in cost.

### Regulatory needs

- i) Controlled definition and change of trial parameters
- ii) Controlled execution
- iii) Blinding and control of operational bias
- iv) Oversight of trial execution (Data Monitoring Committees (DMC))
- v) Audit-ability and real-time inspections

### Industry needs

- i) Ability to handle events and notify users in real-time
- ii) Control of who does what, and when.
- iii) Process: Workflow and Control
- iv) Accessibility
- v) Visibility

## 1. Background

A typical adaptive clinical trial includes one or more interim analysis, allowing the sponsors to stop the trial for efficacy or futility, or adapt the trial and adjust specific , pre-determined parameters like sample size and dose selection. The goal is to accelerate clinical development, improve efficiency, better target experimental therapies to responsive patient groups, and reduce the number of patients exposed to inappropriate or ineffective drugs.

The diagrams below depict the traditional trial design process and the process implemented in ACES.

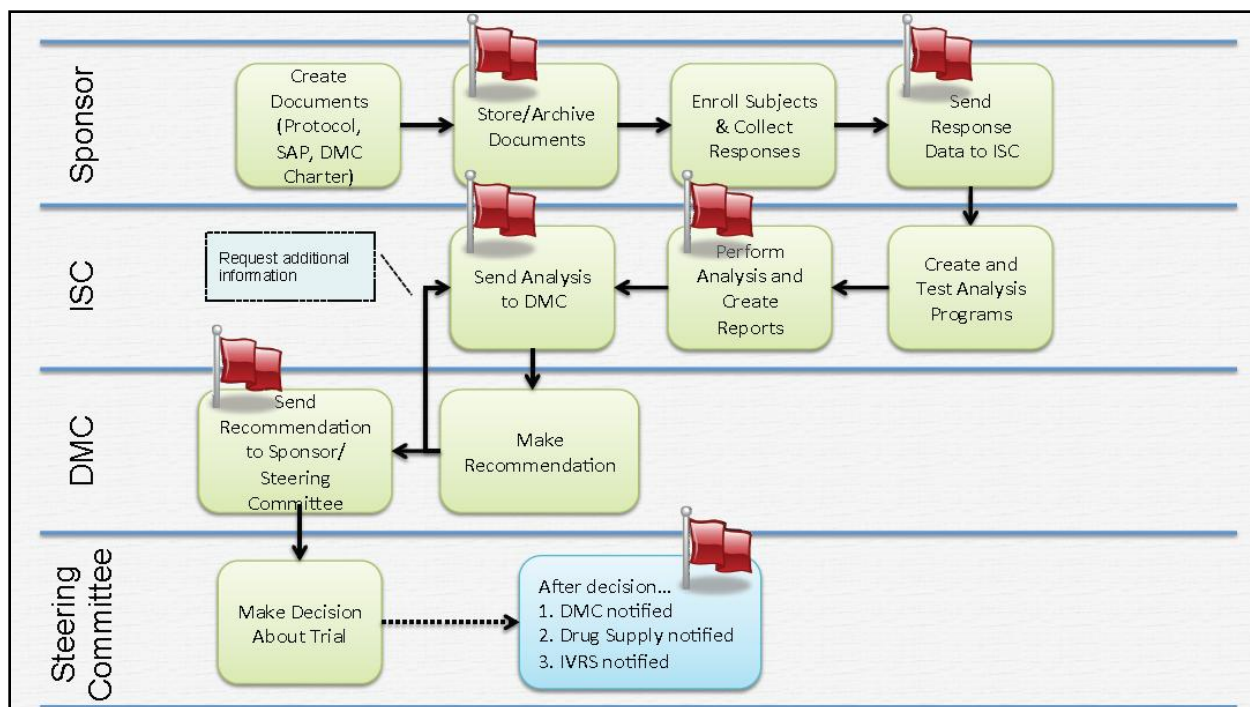


Figure 1: Traditional Trial Workflow

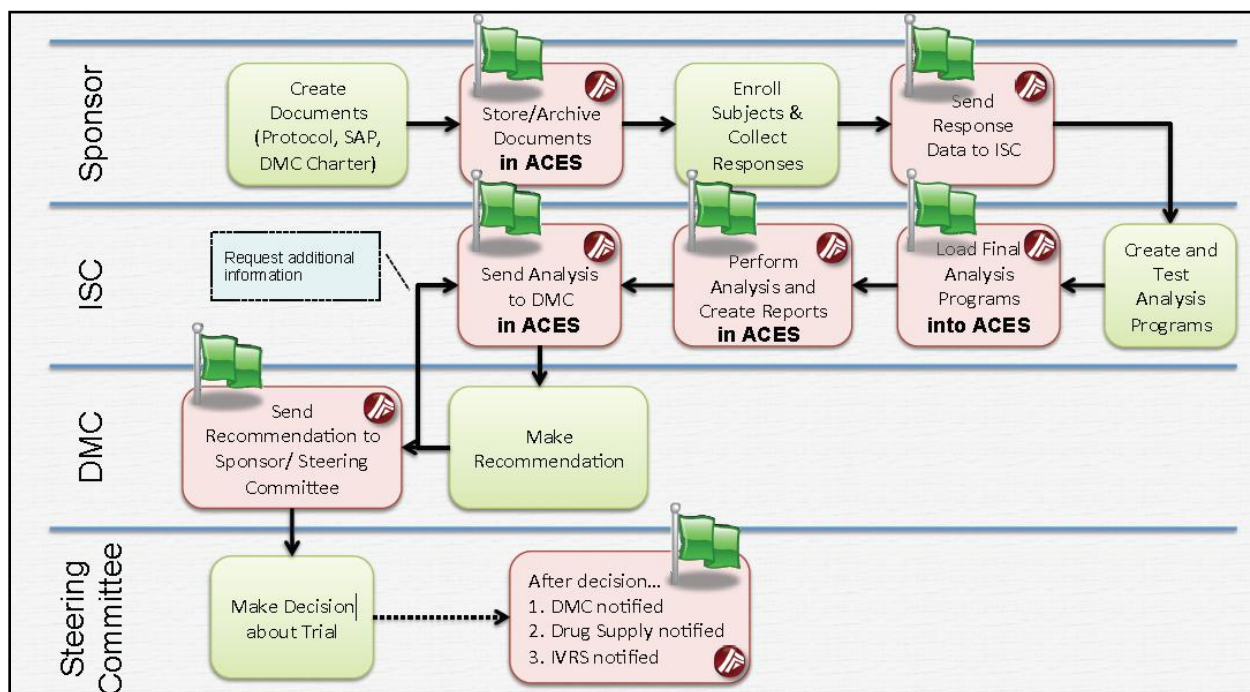


Figure 2: Trial Workflow in ACES

For adaptive clinical trials to be operationally successful, the human resources and processes involved must have greater flexibility and coordination when compared to a traditional trial design. These resources include biostatistics, clinical data management, IVRS, drug supply, etc. The lack of control in a traditional trial leads to a potential for misuse of information that could bias the result of the trial or adapt the trial to bring the drug to market quickly. A comprehensive system like ACES addresses this concern.

ACES a platform which can be integrated into the sponsor's environment and provides:

- Controlled definition and change of trial parameters
- Controlled execution
- Blinding and control of operational bias
- Oversight of trial execution
- Audit-ability and real-time inspections of who does, what and when
- Ability to handle events and real time notifications
- Trial Workflow
- Visibility - each user in ACES has a customized view of the studies based on their assigned role

The following diagram illustrates the different roles that play a role in a clinical trial and the way ACES provides a controlled access to the trial execution and results.

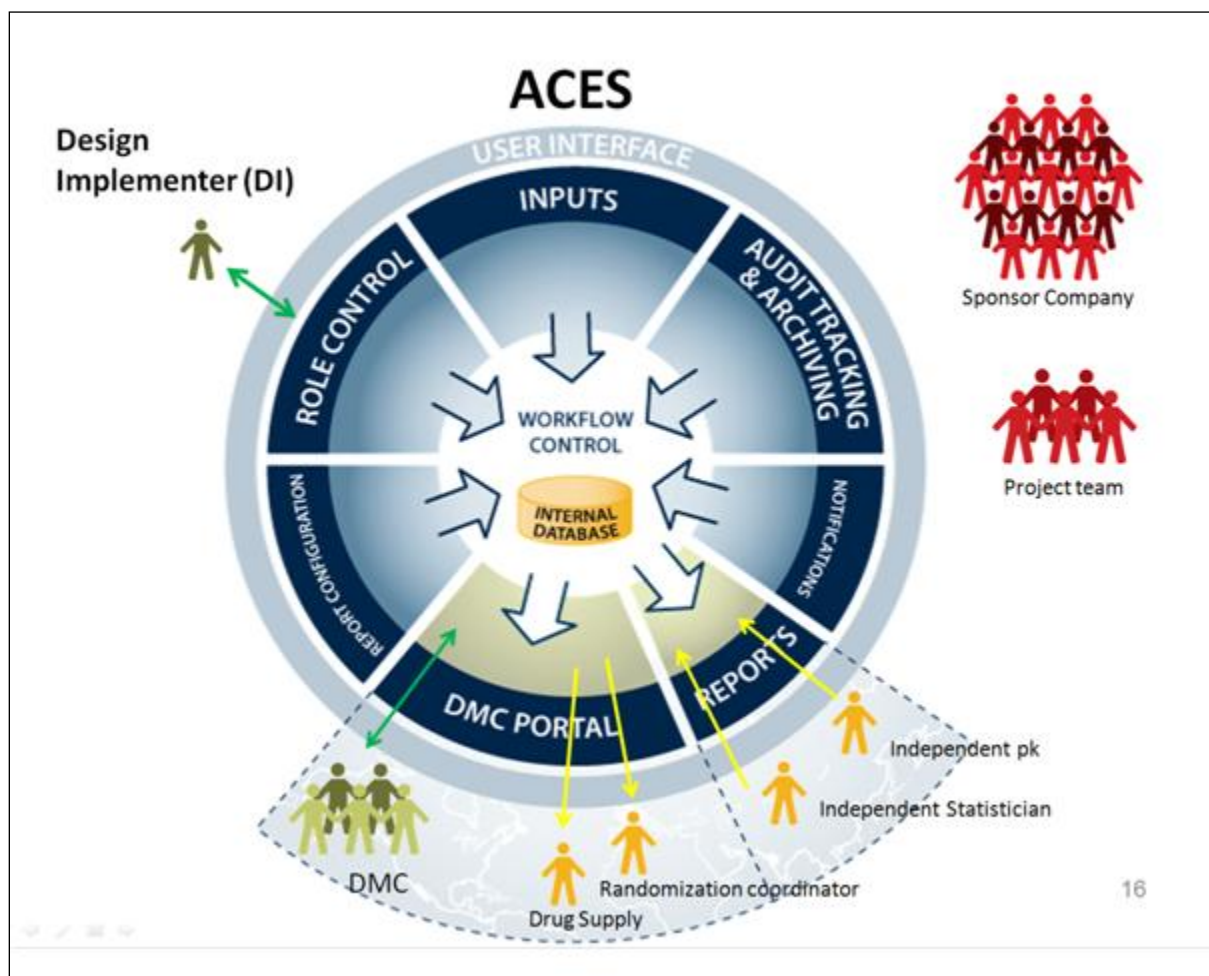


Figure 3: Access Control Execution System

## 2. ACES

### 2.1 Solution Architecture

ACES is designed with the capability be integrated in to the sponsor's current systems with little effort. ACES can be integrated with the sponsor's SAS, authentication, email, and other systems by using shared interfaces and adapters. The component of the system and its integration possibilities are shown in the diagram below.

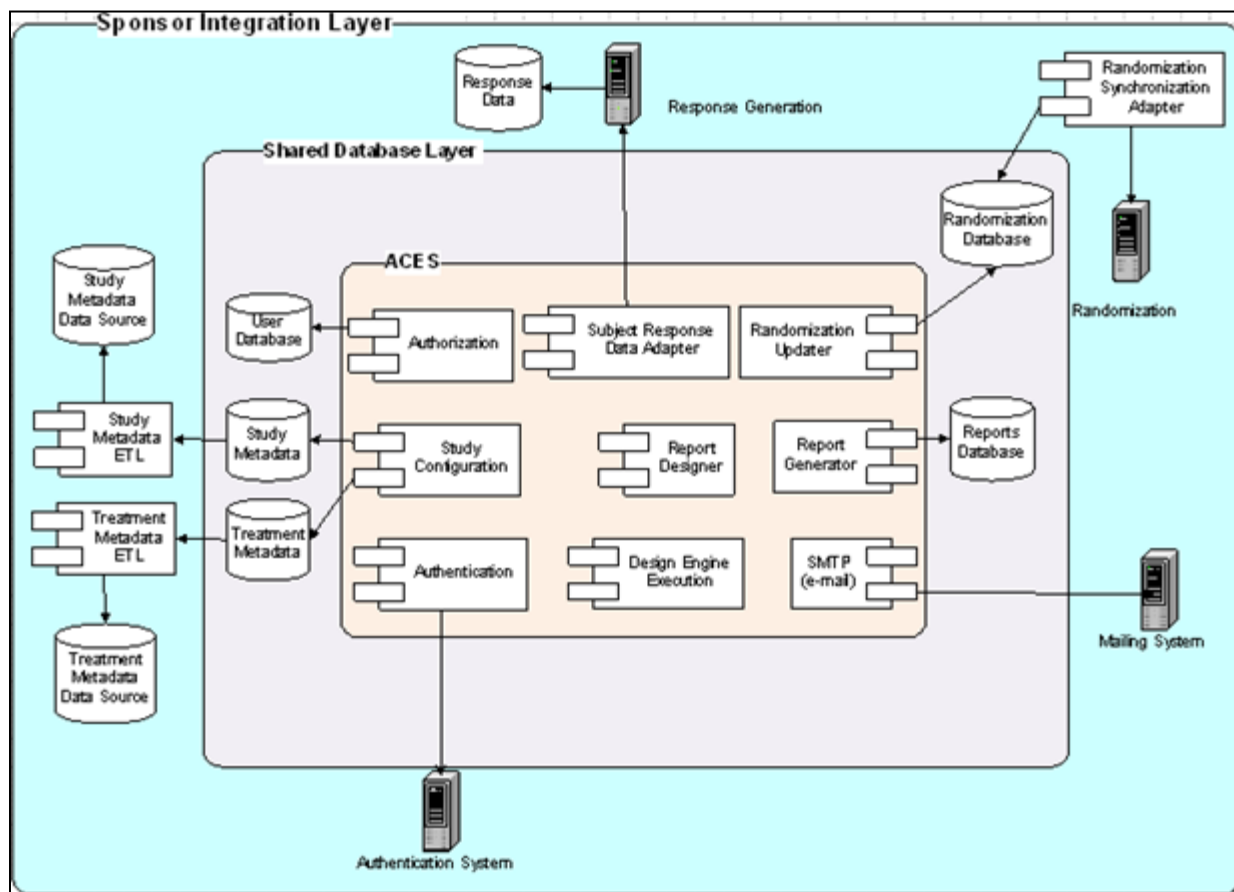


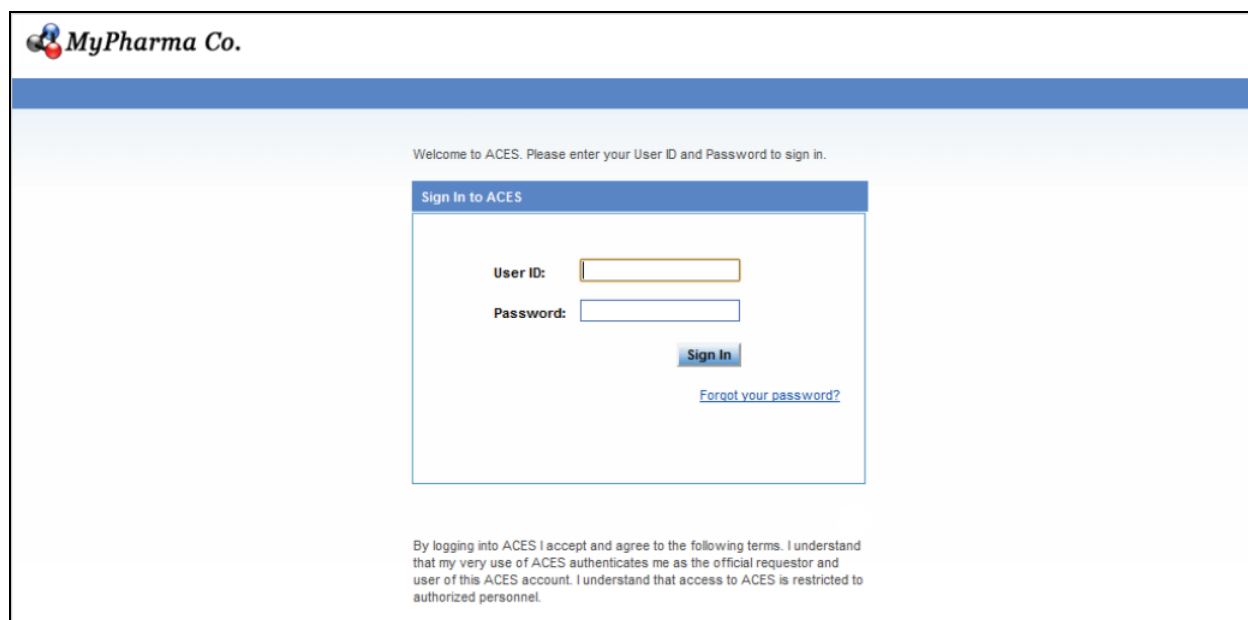
Figure 4: Architectural block diagram

### 2.2 Access Control

ACES uses role-based control to access the different operations within the system. Users are assigned membership to roles to grant access. Predefined roles with specific permissions as well as user-defined roles are supported. Authentication is performed through connection to the enterprise authentication system (e.g., LDAP) and validated at login. The key roles and their permissions are as follows:

- **ACES Administrator (ADMIN):** Administers roles, user enrollment and control, system-wide trial parameters and trial owners.
- **Design Implementer (DI):** Owns a trial design and manages membership to various roles in the trial, trial execution parameters and documents and reports. The DI also performs the execution of the interim analysis, reviews and approves analysis results as well as documents and reports and manages notifications to the users as execution progresses.
- **Data Monitoring Committee (DMC):** Reviews the analysis reports and documents and mediates the approval of the analysis results.
- **Randomization administrator (RAND):** Generates and manages the randomization lists and controls access to the lists to the Drug Supply Coordinator.

- Drug Supply Coordinator (DSC): Manages timely supply and delivery of the drug to the trial sites in conjunction with Randomization Administration.



MyPharma Co.

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.

Figure 5: User Authentication

| Summary                       | Study Setup     | Assign User                                                              | Configure Reports           | Notification Configuration | Document Category     |
|-------------------------------|-----------------|--------------------------------------------------------------------------|-----------------------------|----------------------------|-----------------------|
| <b>Study Role Assignments</b> |                 |                                                                          |                             |                            |                       |
| User                          | User ID         | E-mail                                                                   | Role                        | Account Status             | Last Login Time (UTC) |
| Shailesh Kulthe               | Shailesh.Kulthe | <a href="mailto:Shailesh.Kulthe@Cytel.com">Shailesh.Kulthe@Cytel.com</a> | ADI                         | Enabled                    | 02-Sep-2011 08:50:51  |
| Atul Paranjape                | Atul.Paranjape  | <a href="mailto:Atul.Paranjape@Cytel.com">Atul.Paranjape@Cytel.com</a>   | ADI (Backup)                | Enabled                    | 31-Aug-2011 12:22:04  |
| Ketan Godse                   | Ketan.Godse     | <a href="mailto:Ketan.Godse@Cytel.com">Ketan.Godse@Cytel.com</a>         | DMC                         | Enabled                    | 31-Aug-2011 12:35:09  |
| Eric Silva                    | eric            | <a href="mailto:eric.silva@cytel.com">eric.silva@cytel.com</a>           | Randomization Administrator | Enabled                    | 31-Aug-2011 14:46:43  |

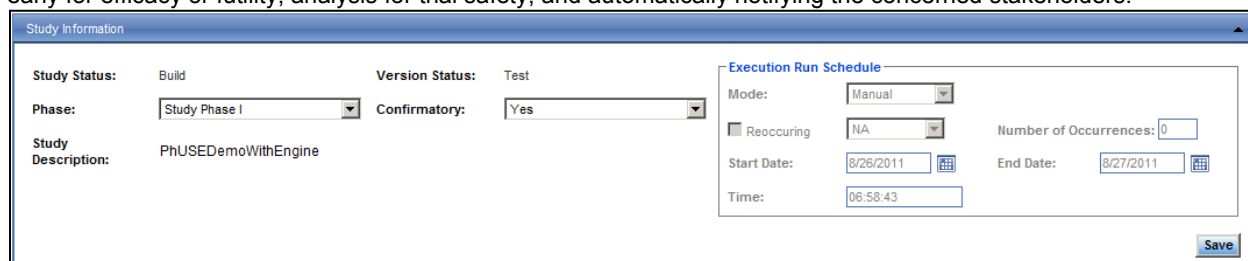
Figure 6: Role Membership and Access Control

## 2.3 Interim Analysis Execution

A well-managed interim analysis execution workflow includes features allowing the user to: plan the interim analysis execution; execute statistical programs associated with the interim analysis; access response data; generate recommendations, reports and randomization lists; and notify users of new activity in the system.

### Interim Analysis Setup

The DI performs the configuration of interim analysis execution events. Execution cycles can be configured to start automatically or manually. The configuration of the interim analysis execution event includes association of the statistical programs, notifications of the completion of the executions and generation of the reports. Automatic execution is especially helpful to users, allowing them to schedule periodic execution of analysis for stopping the trial early for efficacy or futility, analysis for trial safety, and automatically notifying the concerned stakeholders.



**Study Information**

Study Status: Build      Version Status: Test

Phase: Study Phase I      Confirmatory: Yes

Study Description: PhUSEDemoWithEngine

**Execution Run Schedule**

Mode: Manual

☐ Reoccurring      NA      Number of Occurrences: 0

Start Date: 8/26/2011      End Date: 8/27/2011

Time: 06:58:43

Figure 7: Execution Run Schedule Configuration

## Execution Dashboard

The execution dashboard provides a summary of interim executions for the trial. The DI can view the summary of the execution and its current status.

Study ID: PhUSEDemoWithEngine Study Version: V1.0 Current Version Status: Test

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                                                                             |
|------------|----------------------|---------------|----------------|---------------------------|-----------------------|----------------------|--------|----------------------|----------------------|--------------------------------------------------------------------------------------------------|
| 4          | 26-Aug-2011 08:51:09 | V1.0          | Test           | Review Pending            | Test Run On Live Data | <a href="#">View</a> |        | <a href="#">View</a> | <a href="#">View</a> | <a href="#">Randomization List</a><br><a href="#">Treatment</a><br><a href="#">Probabilities</a> |
| 3          | 26-Aug-2011 08:46:40 | V1.0          | Test           | Execution Cycle completed | Test Run On Test Data | <a href="#">View</a> |        |                      | <a href="#">View</a> | <a href="#">Randomization List</a><br><a href="#">Treatment</a><br><a href="#">Probabilities</a> |
| 2          | 26-Aug-2011 08:31:37 | V1.0          | Test           | Execution Cycle completed | Test Run On Test Data | <a href="#">View</a> |        |                      | <a href="#">View</a> | <a href="#">Randomization List</a><br><a href="#">Treatment</a><br><a href="#">Probabilities</a> |
|            |                      |               |                |                           |                       |                      |        |                      |                      | <a href="#">Randomization List</a>                                                               |

[Refresh](#)

Figure 8: Execution Dashboard

The interim analysis execution also has features to view inputs and outputs of the interim analysis, view errors that may have occurred during the current execution, and view pending actions for the current interim analysis execution.

## Manual Interim Analysis Execution

The DI may initiate a manual execution of the interim analysis at any time. On completion of execution, the system automatically sends a notification message to the DI.

Study ID: PhUSEDemoWithEngine Study Version: V1.0 Current Version Status: Test [Promote To Active](#)

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

Run Number: 5

Design Engine: DemoEngine.exe

Response Script:

Run Classification: [Select Run Classification](#)

☒ Use User-Supplied Response File

Current User-Supplied Response File:

Import User-Supplied Response File:  [Browse...](#) [Upload](#)

[Run-Time Parameters](#)

Quantity of Randomization numbers to generate(default shown)

[Execute Design Run](#)

Figure 9: Execute Interim Analysis

## Review and Approval of Execution Result

The DI reviews the results of the execution, and chooses to accept or reject the execution. If accepted, the configured roles are notified of the reports generated during the execution cycle.

Every action and decision made by the DI is logged in to the audit trail.



Study ID: PhUSEDemoWithEngine Study Version: V1.0 Current Version Status: Test

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

Run Number: Test-Test Run On Live Data-4

Execution Cycle Date: 26-Aug-2011

**Execution Cycle Review**

☐ Accept ☒ Reject

Note :

Apply

**Apply Randomization List**

☐ Yes ☒ No

Note :

Apply

**Review Reports**

[Review Reports](#)

Figure 10: Interim Analysis Pending Actions

## 2.4 Document Portal

The document portal in ACES helps to maintain trial documents such as protocol, DMC meeting notes, generated interim reports, and user uploaded documents in a central location. Access to the documents is controlled by user roles and each document access is audited. This addresses the regulatory concern of controlling and documenting access to trial information and documentation to minimize the potential of operational bias being introduced.

Users are able to view the documents assigned to them from the document dashboard. Notifications are sent when documents are assigned to users.

**MyPharma Co.** Sign Out

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

Study: ALC-123 Current Version: V1.0 Study State: Open ADI Name: Albert

Last Execution Cycle Run: Active-Interim Analysis-2 Last Execution Cycle Run Date: 11-Feb-2011

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> <small>NEW</small> | Protocol Documents | Study Protocol                         | Stephen     | 14-Feb-2011 21:45:41 |
| <a href="#">DMC Charter</a> <small>NEW</small>    | Protocol Documents | DMC Charter                            | Stephen     | 14-Feb-2011 21:45:39 |
| <a href="#">SAP Document</a> <small>NEW</small>   | Protocol Documents | Statistical Analysis Plan              | Stephen     | 14-Feb-2011 21:45:30 |

Displaying Items 1 - 4 of 4

Figure 11: Document Dashboard

## Add Supporting Documents

Figure 12: Add/Import Document

Users associated with the trial can upload additional documents into the document portal and specify the roles that should be assigned viewership of the document.

## Reviewing and Approving Supporting Documents

When a new document is uploaded or a new report is generated, a notification is sent to the DI instructing them to review and approve it. Once a document is approved, users in the associated roles are notified about the availability of the document. The DI also has the ability to reject a document or modify the access rights for existing documents.

| Select                | Document Name                                 | Category   | Description                                           | Uploaded By | Date Uploaded        | Execution Cycle Run | Marked As | Delegate To |
|-----------------------|-----------------------------------------------|------------|-------------------------------------------------------|-------------|----------------------|---------------------|-----------|-------------|
| <input type="radio"/> | <a href="#">DMCCharterforConfirmatoryA...</a> | Dmc Report | DMC Charter for Confirmatory Adaptive Clinical Trials | Ketan       | 31-Aug-2011 12:36:39 | Study Documents     | Uploaded  | ADI;DMC     |

Figure 13: Document Review

## 3. Regulatory Audits

A trial has the potential to change after an interim analysis. One of the main regulatory requirements is to track trial changes, document why the change was made, and be able to provide evidence and documentation supporting the change.



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ACES logs every change made to the trial to an audit trail with the identity of the person making the change and the reasons. Also logs user access and action. Point in time snapshots is maintained at each interim execution allowing regulators to replay the execution and validate the results.

The audit trail can be queried to view specific events, user actions, changes or the entire history of a trial.

Study Log Viewer

Context

Study Level

User ID

Select a user

Date From

To

Study ID

PhUSEDemoWithEngine

Study Version

V1.0

Run Cycle Number

Test-Test Run On Live Data-4

View Report

Generate PDF Report

|   | Time Stamp           | User ID | Study ID            | Action                         | Description                        | Reason For Change                  |
|---|----------------------|---------|---------------------|--------------------------------|------------------------------------|------------------------------------|
| 2 | 8/26/2011 8:51:10 AM | eric    | PhUSEDemoWithEngine | Execution-Design-Details-Saved | Run Execution Design Details Saved | Run Execution Design Details Saved |
| 2 | 8/26/2011 8:51:25 AM | eric    | PhUSEDemoWithEngine | Update_Execution_Status        | Update Execution Status            | Update Execution Status            |
| 2 | 8/26/2011 8:51:26 AM | eric    | PhUSEDemoWithEngine | Update-Execution-Queue         | Execution Queue status updated     | Execution Queue status updated     |
| 2 | 8/26/2011 8:51:26 AM | eric    | PhUSEDemoWithEngine | Update_Response_Generat...     | Response Generation dates Updated  | Update Response Generation Dates   |
| 2 | 8/26/2011 8:51:34 AM | eric    | PhUSEDemoWithEngine | Update_Response_Generat...     | Response Generation dates Updated  | Update Response Generation Dates   |

Figure 14: Audit Trail View

The audit trail can be exported as a PDF document for offline reading and submission to auditors.

| Document Access Log Summary: 12     |                               |                 |          |
|-------------------------------------|-------------------------------|-----------------|----------|
| Document: Alcohol Dependency Report | Created On: 09-Feb-2011 15:39 | UTC             |          |
| Accessed on                         | Accessed by                   | Uploaded by     | Status   |
| 09-Feb-2011 15:40 UTC               | Albert Einstein               | SYSTEM          | ACCEPTED |
| 09-Feb-2011 15:45 UTC               | David Gilmour                 | SYSTEM          | ACCEPTED |
| Document: Alcohol Dependency Report | Created On: 10-Feb-2011 17:22 | UTC             |          |
| Accessed on                         | Accessed by                   | Uploaded by     | Status   |
| 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 |
| Document: Alcohol Dependency Report | Created On: 11-Feb-2011 18:46 | UTC             |          |
| Accessed on                         | Accessed by                   | Uploaded by     | Status   |
| 11-Feb-2011 18:48 UTC               | Albert Einstein               | SYSTEM          | ACCEPTED |
| Document: SAP Document              | Created On: 14-Feb-2011 21:45 | UTC             |          |
| Accessed on                         | Accessed by                   | Uploaded by     | Status   |
| 14-Feb-2011 21:45 UTC               | Stephen Hawking               | Stephen Hawking | ACCEPTED |
| Document: DMC Charter               | Created On: 14-Feb-2011 21:45 | UTC             |          |
| Accessed on                         | Accessed by                   | Uploaded by     | Status   |
| 14-Feb-2011 21:45 UTC               | Stephen Hawking               | Stephen Hawking | ACCEPTED |

Figure 15: Audit Trail Report

## 4. Conclusion

Centralized execution control software like ACES provides the following benefits.

- Provide a platform that can standardize the workflow of clinical trial execution increasing the efficiency and the capability to perform more trials.

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- Increases the capability of Design Implementers to manage multiple studies.
- Provide centralized view to the sponsors of the progress of trials.
- Address regulatory concerns of tracking trial changes, operational bias and auditability.
- Improves communication of users and increases visibility for trial documents for users by sending notifications when changes occur.

## References

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