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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.

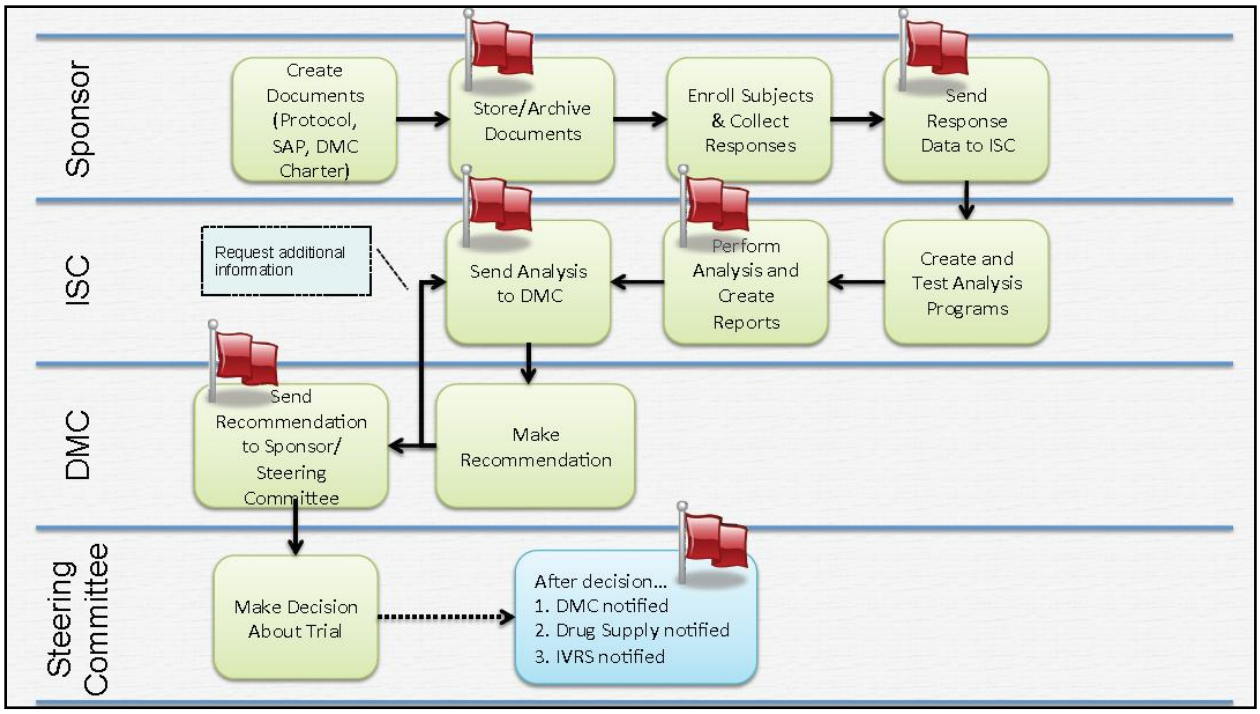

Figure 1: Traditional Trial Workflow

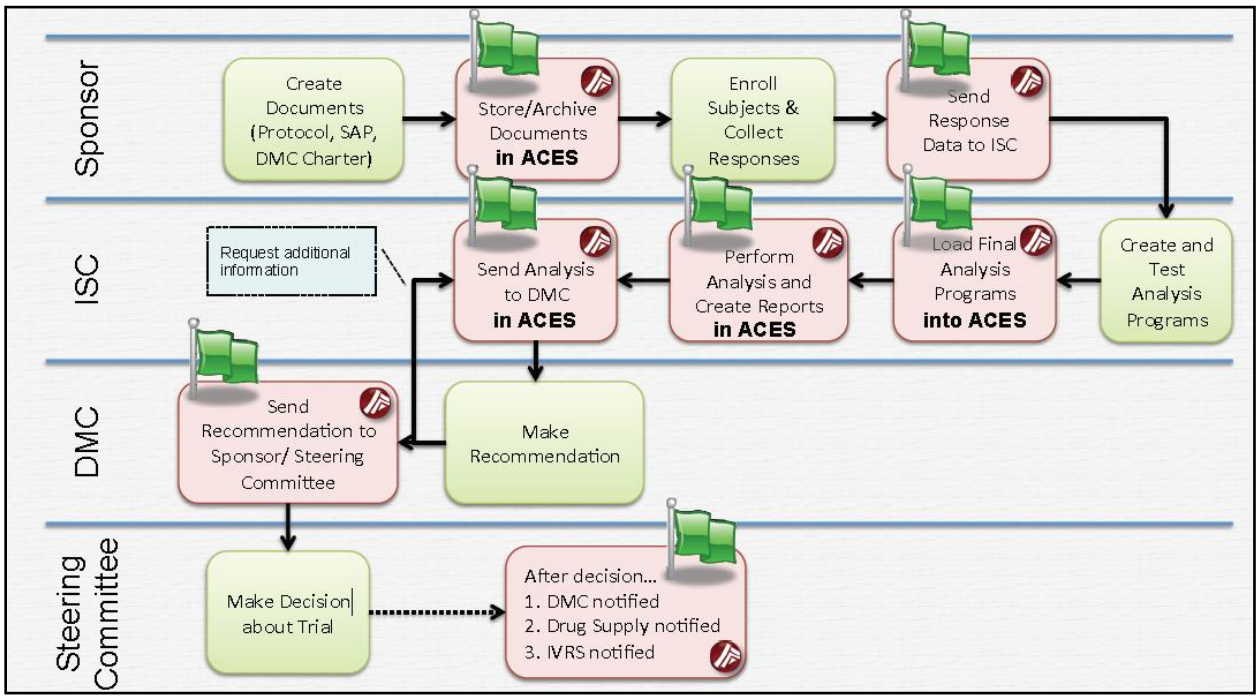

Figure 2: Trial Workflow in ACES

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 trail 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 trail execution and results.

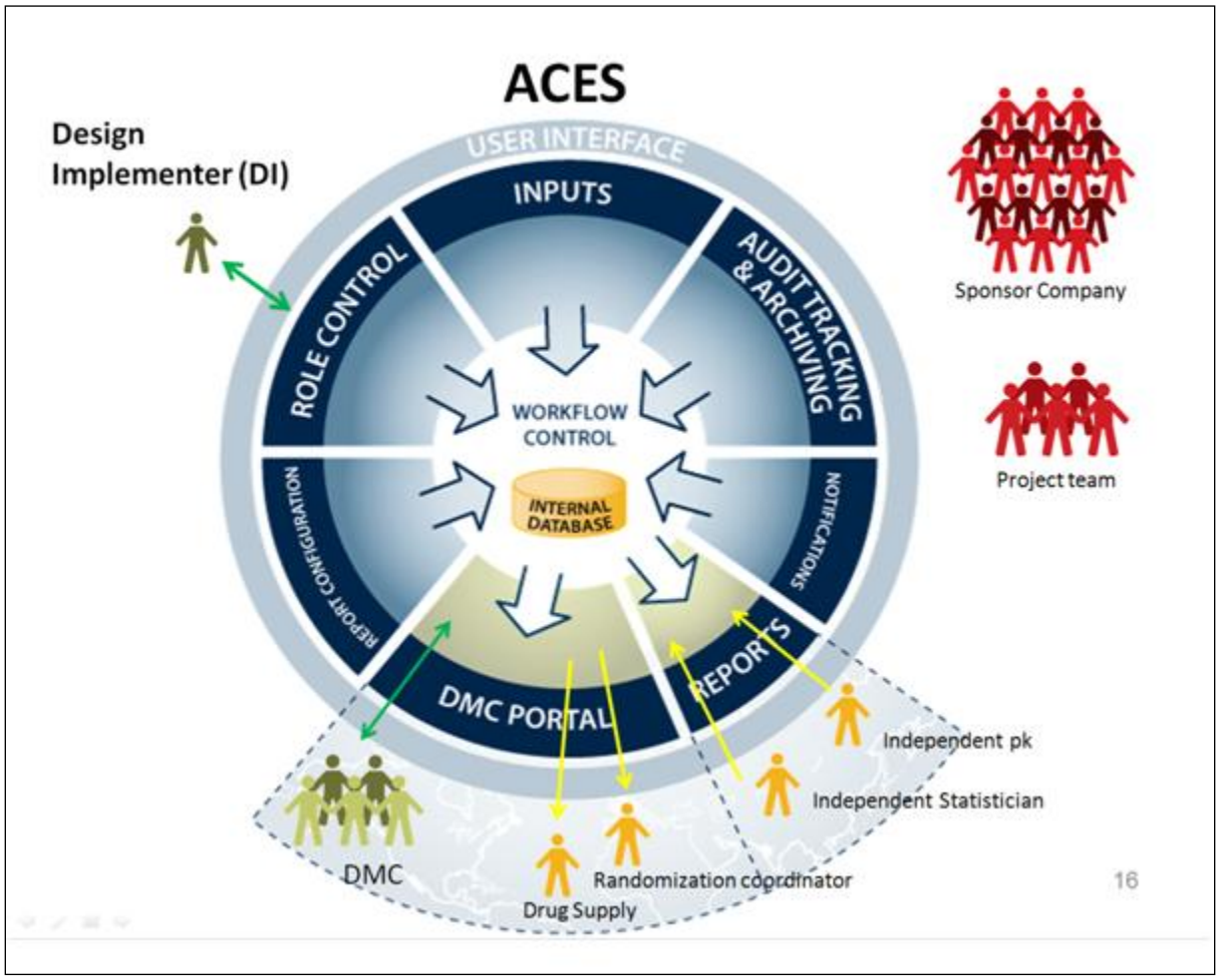

Figure 3: Access Control Execution System

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.

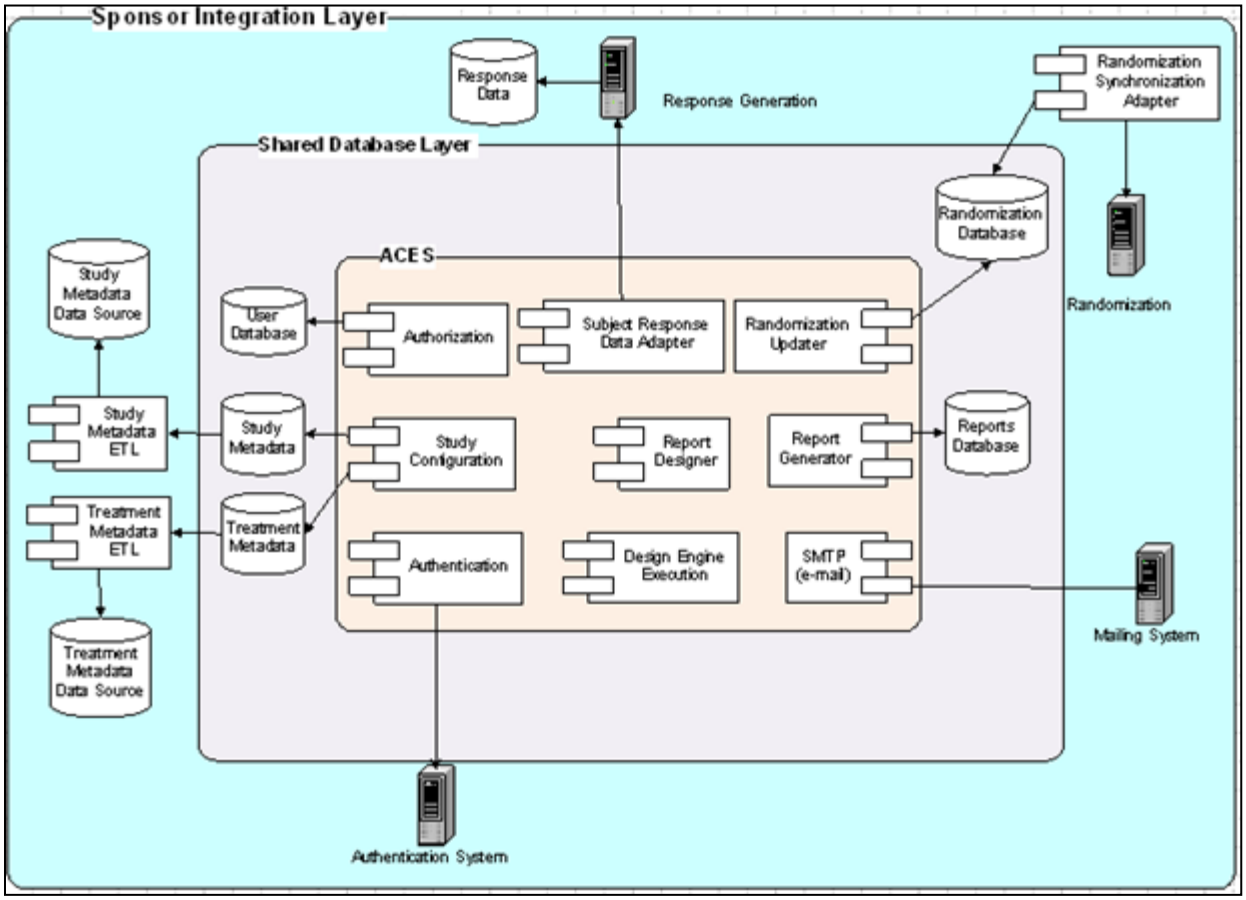

Figure 4: Architectural block diagram

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.

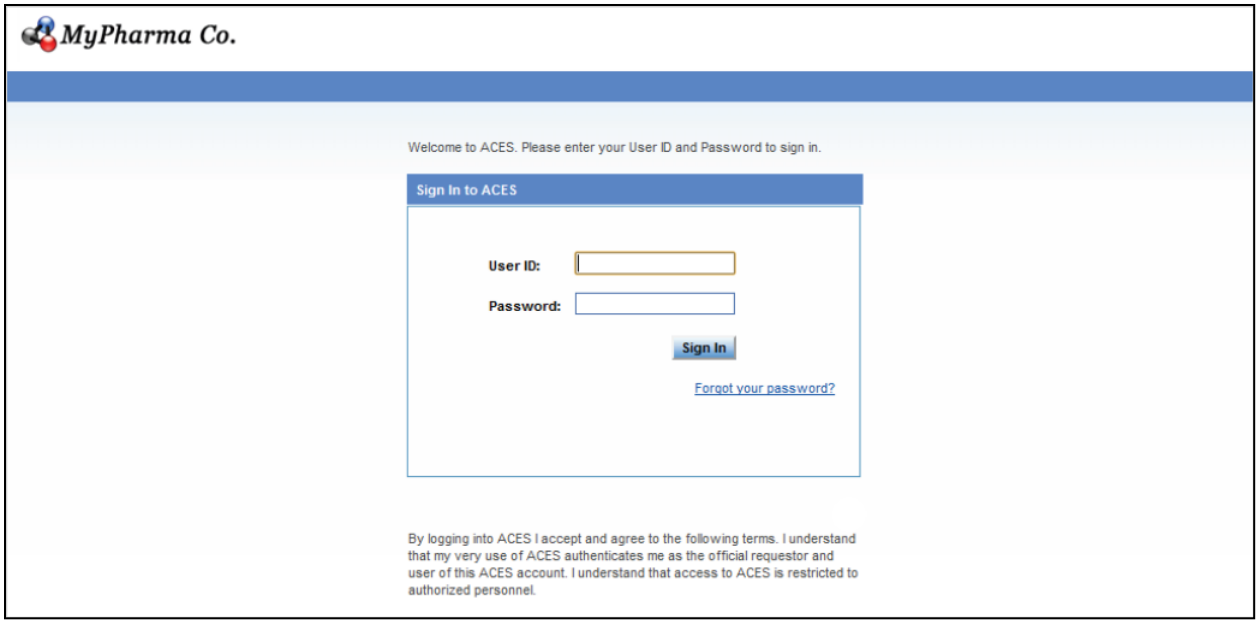

Figure 5: User Authentication

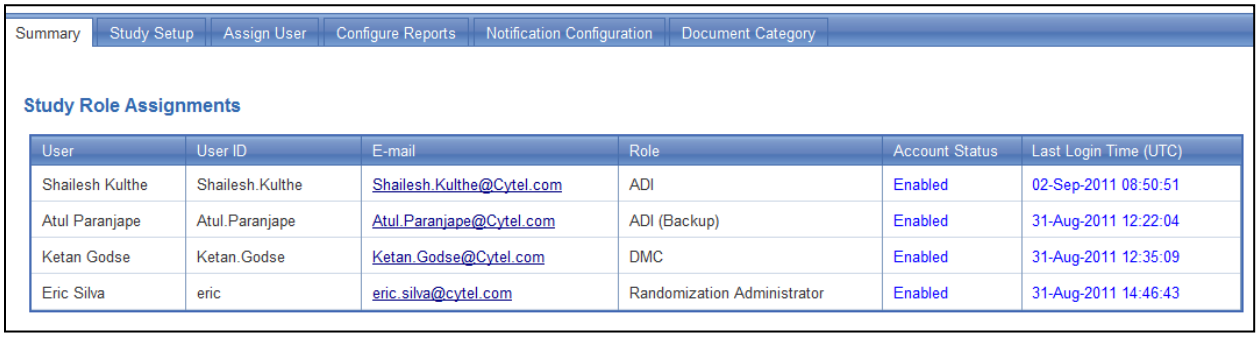

Figure 6: Role Membership and Access Control

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.

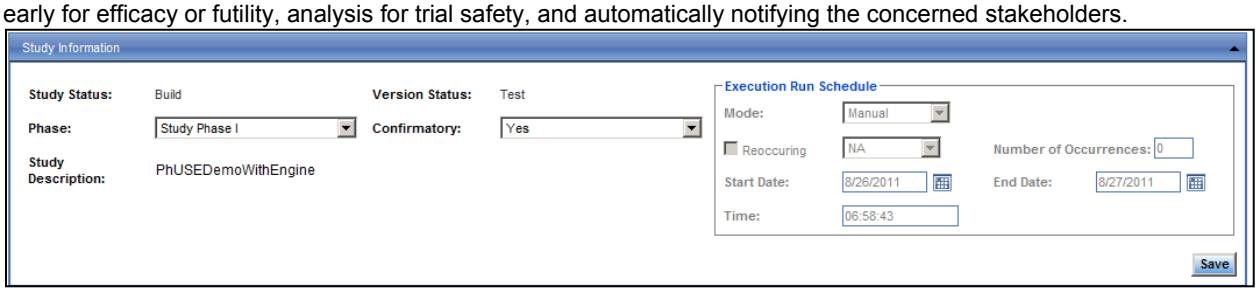

Figure 7: Execution Run Schedule Configuration

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.

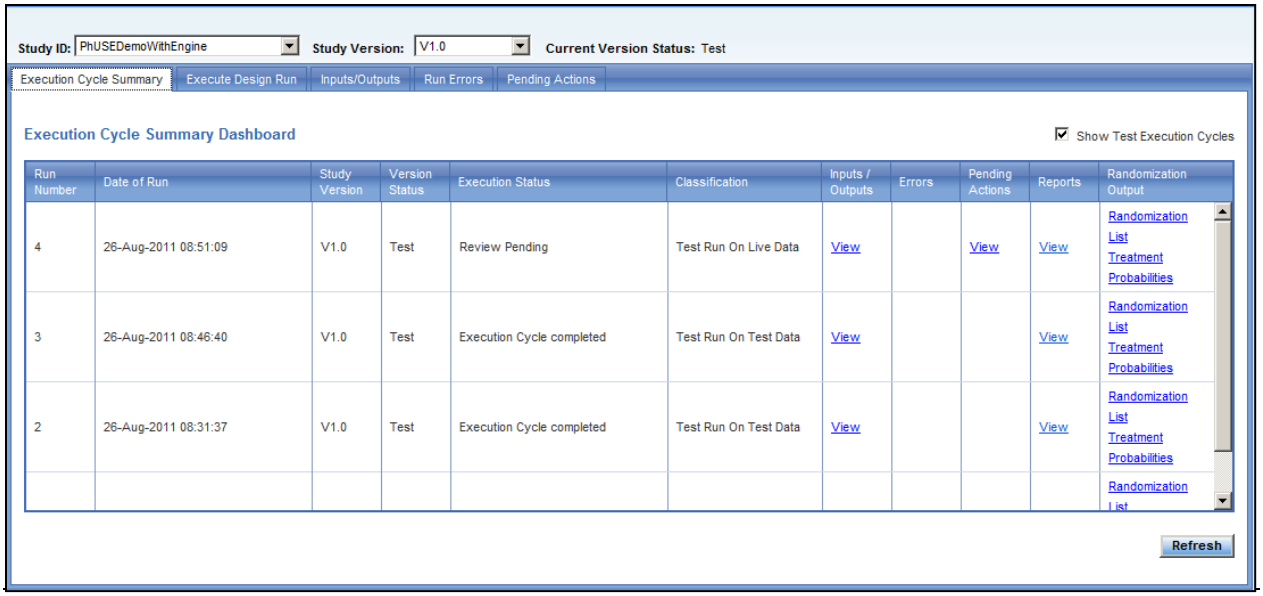

Figure 8: Execution Dashboard

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.

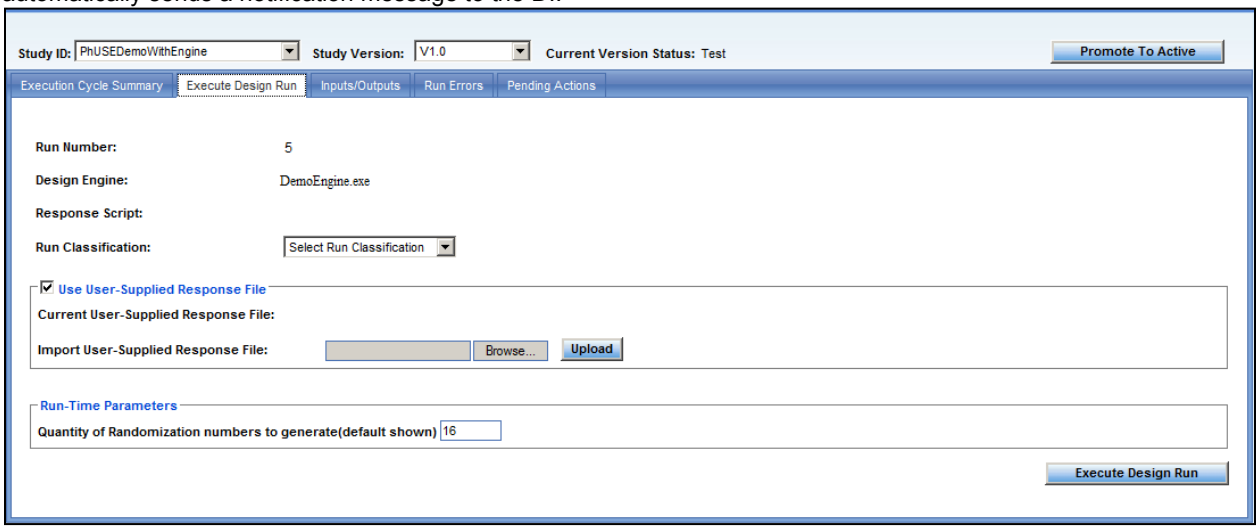

Figure 9: Execute Interim Analysis

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.

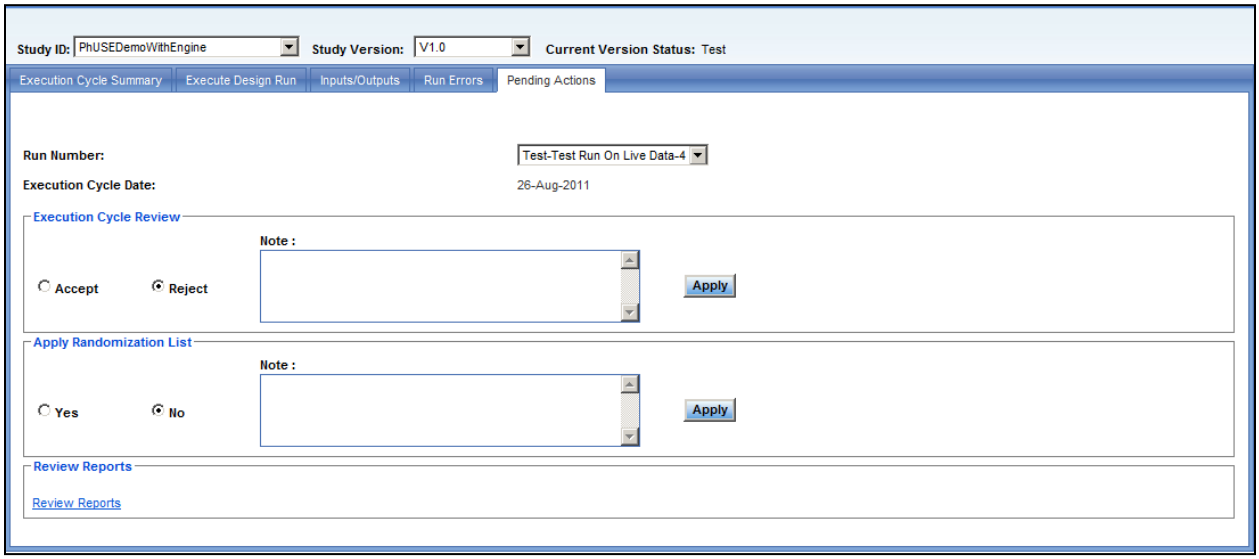

Figure 10: Interim Analysis Pending Actions

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.

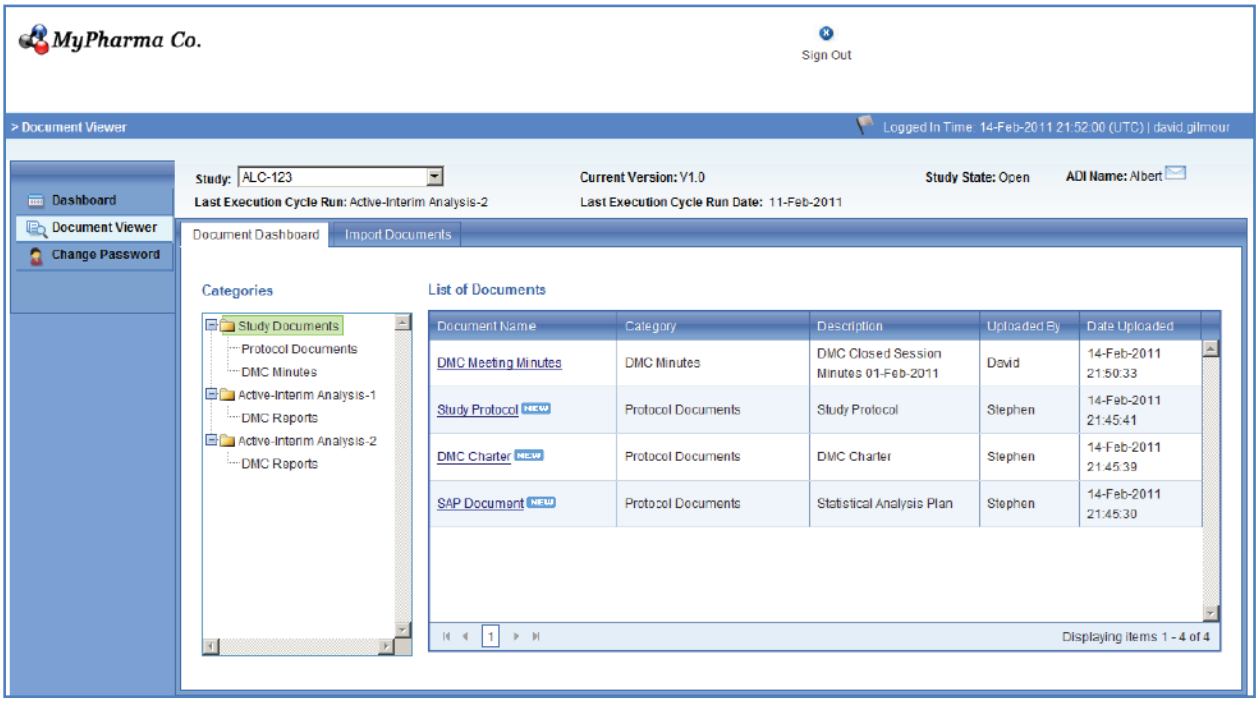

Figure 11: Document Dashboard

Add Supporting Documents

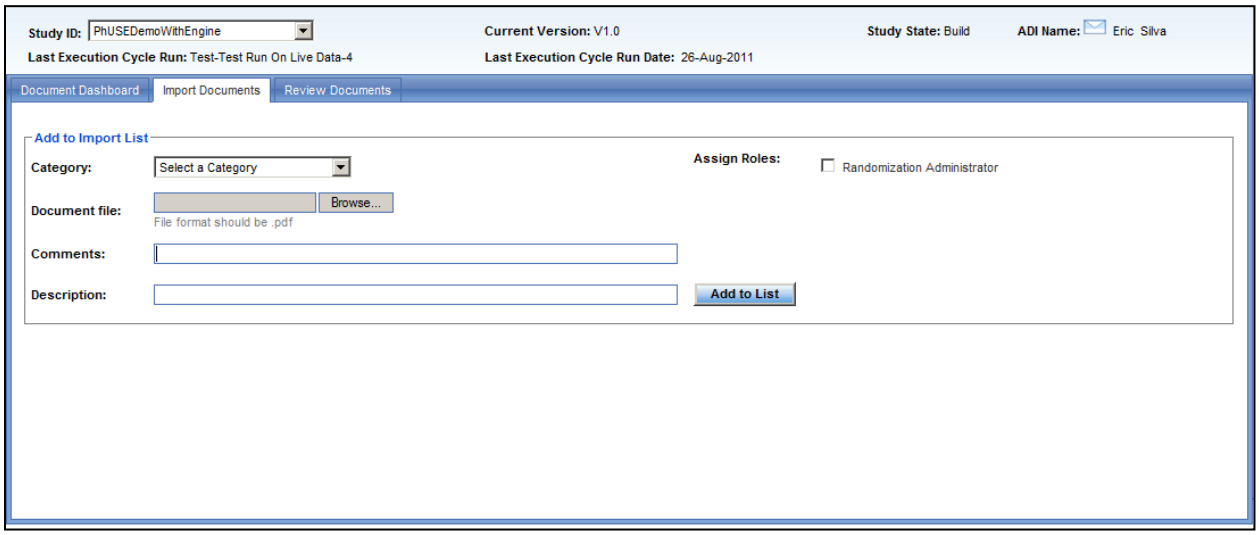

Figure 12: Add/Import Document

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.

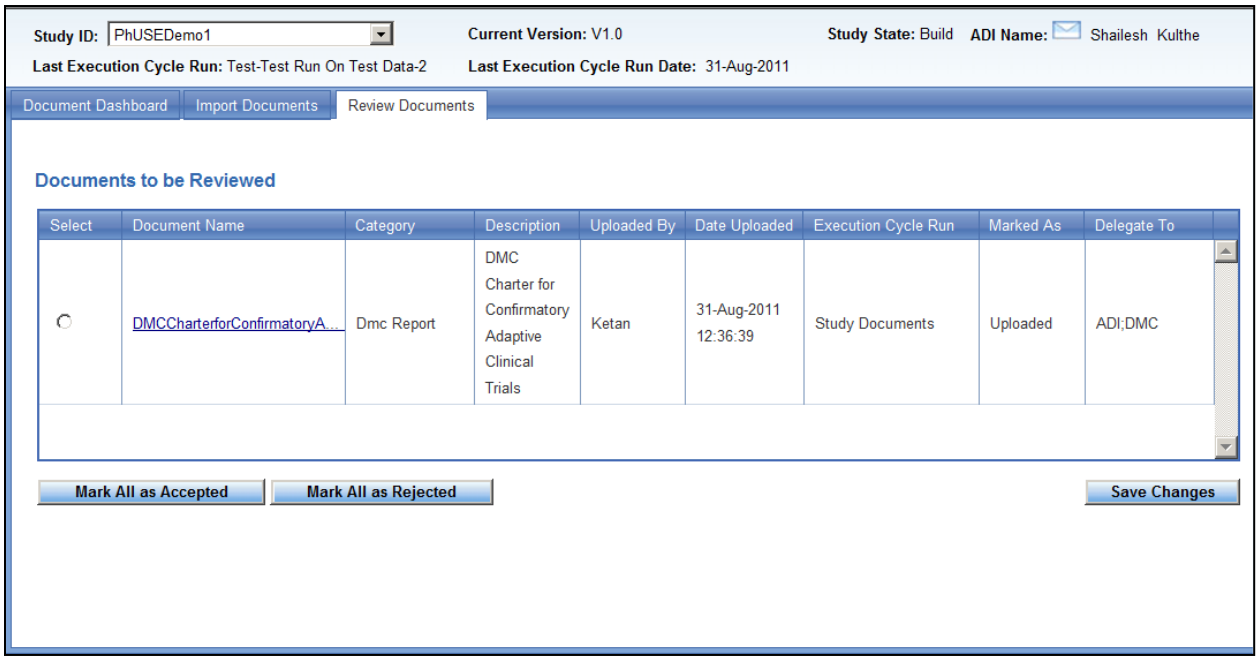

Figure 13: Document Review

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.

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.

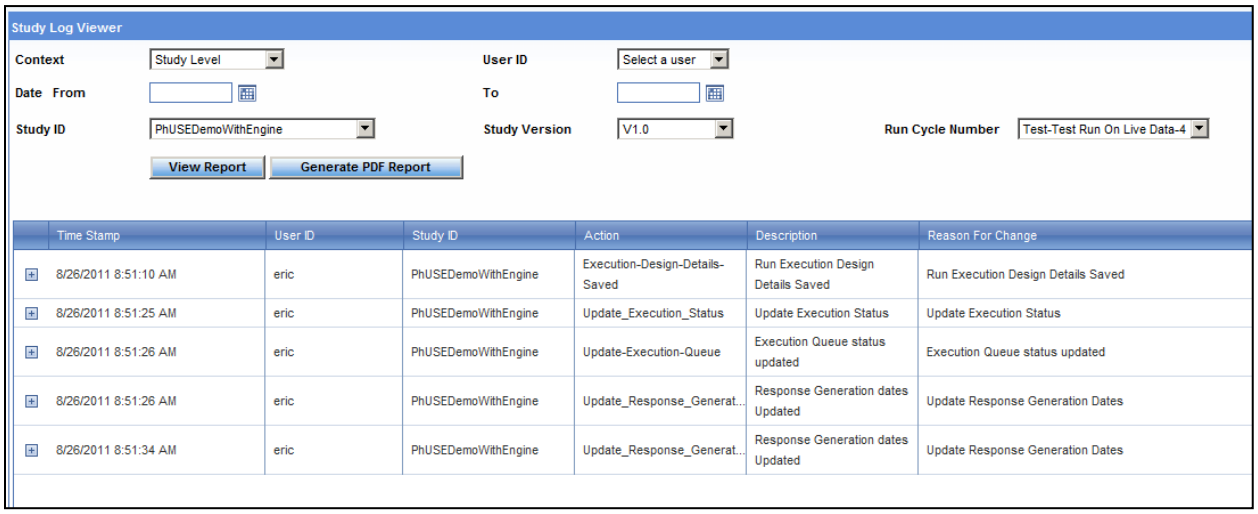

Figure 14: Audit Trail View

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

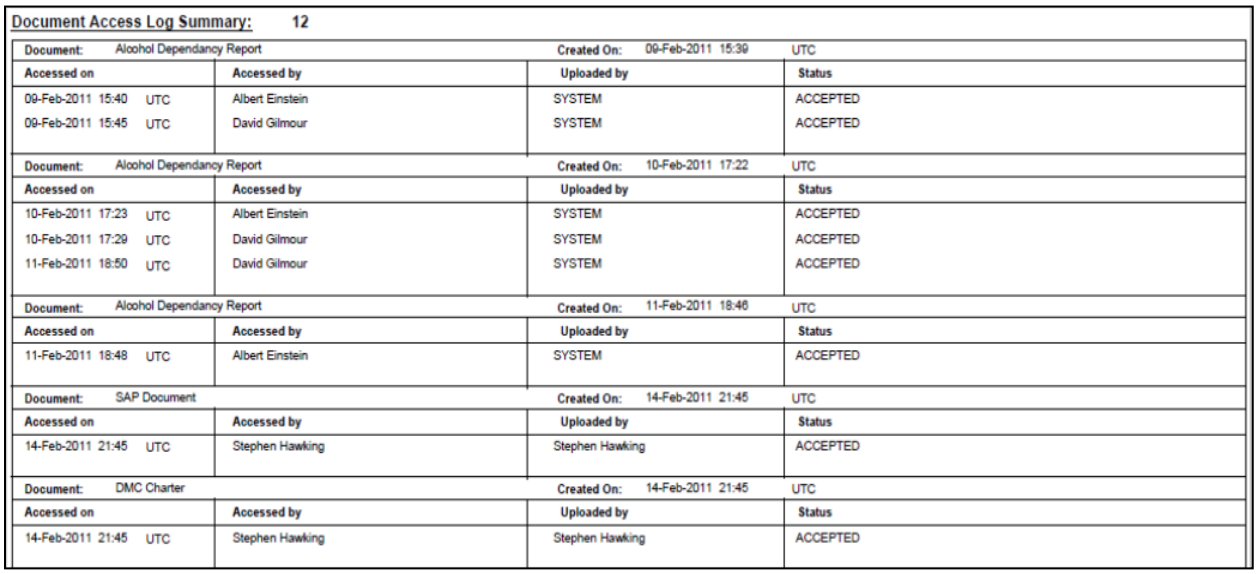

Figure 15: Audit Trail Report

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.

- 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.

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