ACES – A Cytel White Paper

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Abstract

In the past decade, there has been a significant increase in the use of Data Monitoring Committees (DMC) and Adaptive Designs (AD) in clinical trials. While the monitoring of safety data by a formal committee is not required for all clinical trials, it has become the norm to have a formal DMC conduct periodic safety reviews for any controlled trial that evaluates treatments intended to prolong life or reduce risk of major adverse health outcomes, or for trials that compare rates of mortality or major morbidity. Confirmatory, pivotal, and adaptive design trials have more complex operational issues requiring an external and independent DMC. The DMC may have access to unblinded interim data, be required to make expert recommendations about how the trial should continue, and then ensure that planned adaptations are implemented as outlined in the protocol without involving the sponsor or exposing it to unblinded data or results.

This added complexity creates a challenge and a question: how can the DMC, statisticians, and sponsor effectively communicate, share blinded and unblinded data, perform analyses, and implement adaptations without introducing operational bias or compromising the integrity of the trial? One solution is to utilize a sophisticated computer system that can provide the security and necessary firewalls to ensure that interim data is only accessible to those it is intended for, that the rules and processes outlined in the protocol and DMC charter are enforced, and that communication between the DMC and sponsor is effectively facilitated while protecting the integrity of the trial and preventing the introduction of operational bias.

The system must also provide an audit trail that tracks “who saw what and when” providing evidence to regulatory authorities that the protocol was strictly followed with a minimal possibility of bias. This white paper describes the computer system, ACES, which Cytel has built, that makes all of this possible. ACES (Access Control Execution System) has been purpose-built to address the operational complexities inherent in adaptive design and pivotal clinical trials.

Contents

Background

In July 2005 and March 2006, the EMA and FDA, respectively, released guidance documents for the establishment and operational conduct of Data Monitoring Committees for clinical trials. These guidances sent a clear message to trial sponsors that regulatory agencies were concerned about how DMCs were being used, and how processes and policies governing them were being enforced. The response from most trial sponsors was to implement a solution involving a set of complex processes requiring substantial human intervention and the "honor system" of all parties involved.

At the same time, some major advances in clinical trial technology were also occurring. The popularity and reliability of the internet led to traditional IVRS (interactive voice response system) being replaced or augmented by IWRS (interactive web response system), and data collection using traditional paper case report forms (CRF) transitioned to electronic data capture (EDC) systems. The adoption and usage of these new IWRS and EDC systems allowed data to be collected and made available to the trial sponsor for analysis in near real-time. Clinical data collection and entry that used to take several weeks was now possible in a few days.

Adaptive design clinical trials have been around for decades, but the technology and operational support to effectively implement them has not been. The expedited availability of the interim clinical trial data due to IWRS and EDC has made the wide-spread adoption of response-adaptive clinical trials a reality. In 2005, a PhRMA Working Group on adaptive clinical trial designs was formed to investigate and facilitate opportunities that would widen the acceptance and usage of adaptive design. A major goal of this working group was to identify and address the operational, procedural, and statistical challenges associated with implementing adaptive designs.

Over the next five years, the group published many articles and spoke at numerous events about their findings. In March 2006, the EMA released a reflection paper concerning the usage of 'flexible' design confirmatory clinical trials. With the concept of adaptive design still in its

infancy, the paper acknowledged the growing knowledge of adaptive design within the industry, and gave a positive signal that regulatory agencies were accepting of them. In February 2010, FDA released their draft guidance on adaptive design clinical trials. The FDA document was more comprehensive; covering concerns with unblinded analyses, and operational and statistical biases in both early and confirmatory trials. The issuance of this guidance was well-received by industry, and due to the positive position of FDA towards adaptive design, has opened the door for trial sponsors and industry to consider, favor, adopt, and implement adaptive design trials.

Market Review

During an interim analysis both blinded and unblinded data and reports may be produced. Blinded reports such as enrollment and event accruals can be shared with the sponsor and trial operations teams, but unblinded analysis including safety and efficacy information must be restricted to only the DMC and other unblinded users (e.g., ISC). In the case of adaptive design clinical trials, there may also be unblinded randomization adaptations or drug supply reports that need to be shared with the respective teams. The ability to ensure that the right information is getting to the appropriate individuals becomes an important and mandatory requirement for trials with interim analyses.

Current data and statistics [2010] show that IWRS now dominates 80% of the earlier IVRS market, and EDC is now used in over 90% of clinical trials. With IWRS and EDC having become the dominant interfaces, clinical trial sponsors no longer have the burden of getting quick access to interim clinical data; a major hurdle when implementing adaptive design. Trial sponsors now have the ability to design and implement clinical trials that include interim analyses, leading to better decisions about how to move forward with the trial.

As stated before, interim analyses may often involve the analysis and review of unblinded data. As shown in the EMA and FDA guidances, this introduces a major regulatory concern by increasing the risk of operational bias, and can adversely affect the integrity of the trial. It also leads to the logical question, “How can we share, review, and communicate these unblinded results without exposing the sponsor; and how can we provide evidence to regulatory agencies that we have enforced our processes and controlled access to sensitive information?”

As with their response towards the regulatory guidances on DMC conduct, sponsor companies have approached adaptive design by relying on a system of complex processes involving standard operating procedures (SOP), DMC charters, substantial human intervention and an “honor system” of all parties involved to protect the distribution and sharing of unblinded data and analyses.

More recently, an increasing number of pharmaceutical companies of all sizes are investigating or investing in the use of new technologies that facilitate the sharing of information and data for use during interim analysis and periodic review for safety. This is especially true for adaptive design and/or confirmatory trials that make use of an external and independent DMC. These new technologies also allow companies to securely share specific information with external

partners such as DMCs and Independent Statistical Centers (ISC) without having to grant access to their internal corporate network. As adaptive design implementation grows and the usage of DMCs continues to expand, enabling technologies used to facilitate data review and interim analysis are becoming a 'must-have' in a pharmaceutical company's IT toolbox.

Information Sharing Platforms

Most companies have come to understand the value in having information sharing platforms or content management systems (CMS). They may have invested in EMC Documentum eRoom, Microsoft SharePoint, or other content management or document management system. These technologies have proven invaluable; allowing users all over the globe to access the same information no matter where they are.

As useful as these platforms are, they have several deficiencies that make them unsuitable or burdensome for use with clinical trial data. The lack of a clear audit trail is a key feature missing in all commercial platforms. There may be an audit trail or access log, but it often requires IT involvement to obtain, and may not be in a clear, readable format. Another deficiency is their lack of clarity about how to control user privileges and role assignments. It is difficult to know what roles have been assigned to users, and what documents they have access to.

The ability to provide a secure, centralized platform to share clinical data and information with easy control of access is a key feature of Cytel's ACES platform. ACES has been designed to address the deficiencies that exist with the older generation platforms.

What is ACES?

At its core, ACES is an information sharing platform. Surrounding that core is a set of features that enable it to be extremely useful and effective in facilitating the administrative and operational tasks required when performing interim analyses.

ACES is also the architectural platform for a number of other utilities and trial optimization products that integrate seamlessly into the ACES framework.

How is ACES Different?

ACES has been specifically designed to address the operational complexities and regulatory concerns with traditional and adaptive design clinical trials that make use of interim analyses; especially those that involve review of unblinded data.

The ACES computer system has been validated as per Good Clinical Practices (GCP) and 21 CFR Part 11 with respect to electronic records. ACES does not currently make use of electronic signatures.

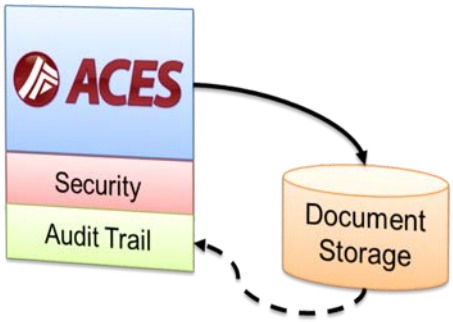
Access

ACES provides a secure, centralized repository for storing and accessing data, information, and documents related to a clinical trial and associated interim analyses. ACES is a web-based platform that can be accessed by anyone regardless of geographic location. This allows both internal trial sponsors and external parties (e.g., DMC, ISC, and IWRS) to access the same information in a controlled and consistent way.

ACES supports all major internet browsers including Internet Explorer, Firefox, Safari, and Chrome.

Security and Control

ACES uses a role-based security model defined at the trial level. Each user is assigned a unique username and password used to access the ACES system. For a given trial, a user may be assigned to one or more roles (e.g., DMC and ISC). The user will then be granted access to information that has been assigned to that role. If a user has access to multiple trials within ACES, the information visible to them will be restricted to the role(s) for the particular trial.



The combination of unique user account and trial specific roles creates a robust, secure firewall ensuring that sensitive data cannot be accessed by unauthorized individuals. This security framework is coupled with an audit trail that records all activity related to: user login, document access, and changes in trial configuration and role assignment. The ACES audit trail is able to be exported as a formatted PDF file at any time to provide assurance of 'who saw what and when.' As evidenced in the regulatory guidance documents, this is a key requirement when conducting interim analyses and implementing adaptive design. These robust firewalls available in ACES do not exist in other technologies such as eRoom and SharePoint.

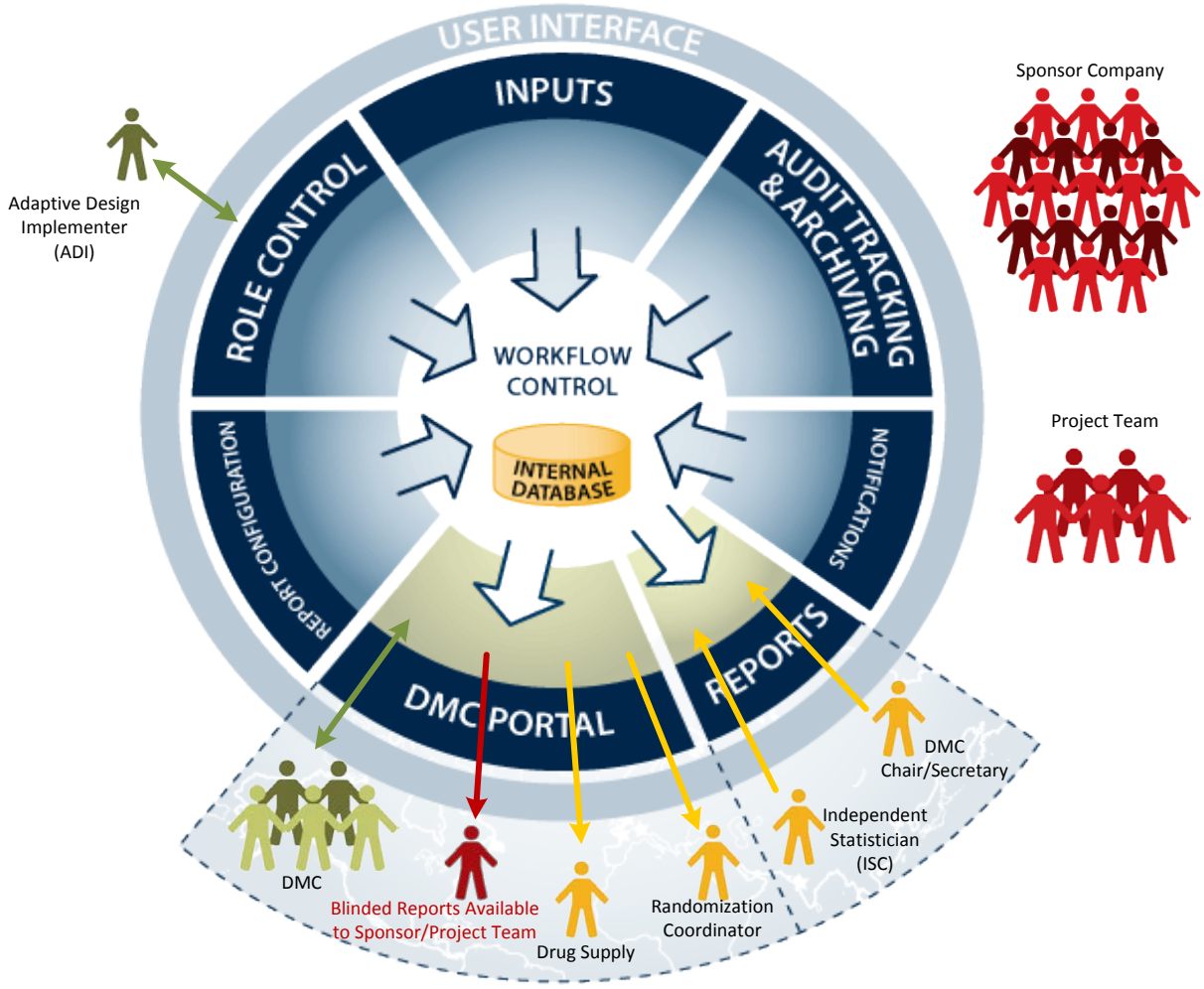
ACES has been designed with the understanding that different roles will be required for the variety of trial sponsors and clinical trial types. ACES is flexible and allows for the customization and addition of roles, as needed. Roles for the sponsor, steering committee, drug supply vendor, and CRO can easily be created and used. In the event the sponsor wants a regulatory agency to have access to certain trial information, a role can be defined allowing restricted access to the agency.

ACES does have a few 'built-in' roles that are common for most trials. Typical of all trials in ACES is the need for someone to administer and configure the trial. User accounts need to be provisioned and assigned to a role(s), and the structure and categories for document and information organization need to be defined. In ACES this role is the Adaptive Design Implementer (ADI). Each trial is configured with a primary ADI and an optional backup ADI who can assume control of the trial in the event the primary ADI is unavailable.

The other default roles in ACES are: DMC, ISC, and Randomization Administrator.

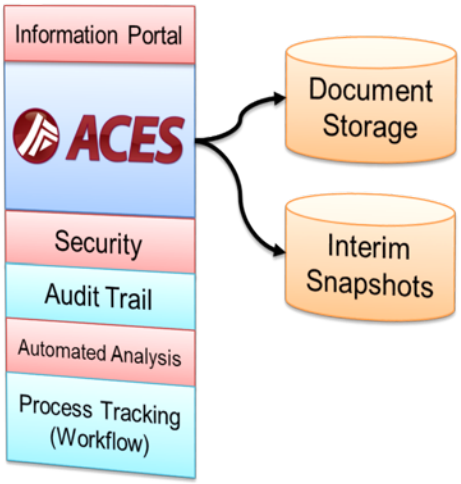
The figure below illustrates the main features of ACES and the typical interaction each user group has with it. The ADI along with the DMC, ISC, and other operational groups can access ACES to store or retrieve information while the project team and other sponsor representatives are restricted (i.e., firewalled) from accessing sensitive information.

All functionality is accessible via a web-based interface. Administrative functions are available to the ADI, while information storage and access is available to the other roles.



Documentation

ACES provides a secure platform to store all clinical trial documents needed for DMC, ISC, IWRS, CRO, and drug supply to carry out their responsibilities as they pertain to data monitoring, interim analysis, safety review, and adaptation decision. Reports, data analytics, enrollment and drug supply forecasting, and other operational artifacts can be stored and securely shared through ACES.



ACES can also be configured to generate analysis reports used during interim or safety analysis. ACES provides the framework to take a snapshot of the data, algorithms, programs, and outputs generated and store them for viewing. This provides a complete chronology of what occurred during the trial without having to be concerned with the burden of

recreating datasets and databases, or finding the programs that were used. ACES also provides a version control system allowing changes to be made without losing the history of what occurred during prior analyses.

All access to documents and data within ACES is logged within the audit trail. Changes to metadata and trial configuration are recorded with a business reason and justification to provide context describing why the change was made.

Trust and Confidence

The ultimate goal of the ACES platform is to provide a solution to trial sponsors that will enable them to build trust and confidence with regulatory agencies when conducting clinical trials that make use of adaptive design and/or unblinded interim analyses. Using ACES as the sole repository for storing and sharing information while the trial is being conducted will provide regulatory agencies with unequivocal assurance that the trial was conducted using a secure, transparent process, and that process was enforced with a clear audit trail showing 'who saw what and when.'

Workflow

As stated before, ACES has been purpose built to understand the workflow associated with conducting clinical trials and interim analyses. This understanding allows ACES to automate many of the common administrative tasks associated with trial operations such as notifying users when new information is available, reminding users when a DMC meeting is scheduled to take place, and sending updated randomization and treatment information to IWRS and drug supply users.

ACES Usage and a Case Study

Since its launch in 2010, ACES has been used in nearly a dozen Phase 2 and Phase 3, adaptive and traditional clinical trials across different therapeutic areas including oncology, central nervous system (CNS), infectious disease, immunology, and psychiatry/psychology.

ACES has also been used with a seamless phase 2/3 adaptive design trial. The trial was designed to randomize subjects equally across four treatment arms; three active treatments and one placebo. An interim analysis was conducted after approximately 100 subjects were enrolled in each arm. The interim analysis consisted of three decision rules:

- Early termination for futility
- Dose selection: select one or two active doses (depending on observed pattern of response rates) in addition to placebo to move forward into the second stage of the trial
- Sample size increase: possible one-time sample size increase based on conditional power for second stage of the trial

The complex rules for dose selection were developed into an executable analysis program that was stored in ACES. In addition, the initial randomization table and treatment codes were independently loaded into ACES.

When the time came to conduct the interim analysis of the primary endpoint, the blinded subject-response dataset was loaded into ACES. ACES combined the blinded dataset with the randomization table and treatment codes to internally construct an unblinded dataset that was then passed to the analysis program to generate a report. The report was assigned to the DMC within ACES. A sample of the report contents are displayed below.

Interim Report Recommendations for ALC-123

Generated on 14-Feb-11 10:16 PM (UTC) by ACES*

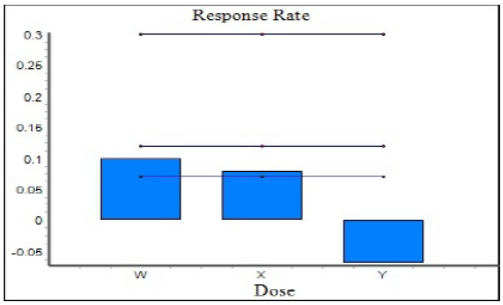
Table 1: Interim Results for Doses

Dose	Response Rate	SE	N
Z	0.233	0.042	100
W	0.332	0.047	100
X	0.312	0.046	100
Y	0.163	0.037	100

Table 2: Interim Results for treatment comparisons

Dose	Response Rate (Difference From Placebo)	SE	CP
W	0.099	0.062	0.633
X	0.079	0.062	0.399
Y	-0.069	0.062	0

Figure 1: Treatment Comparisons & guidelines for efficacy thresholds



Interim Report Recommendations for ALC-123

Recommendations for dose selection in Part B

Based on pre-defined guidelines for dose selection that relate to efficacy only, doses W, X are recommended for continuation in Part B of the study.

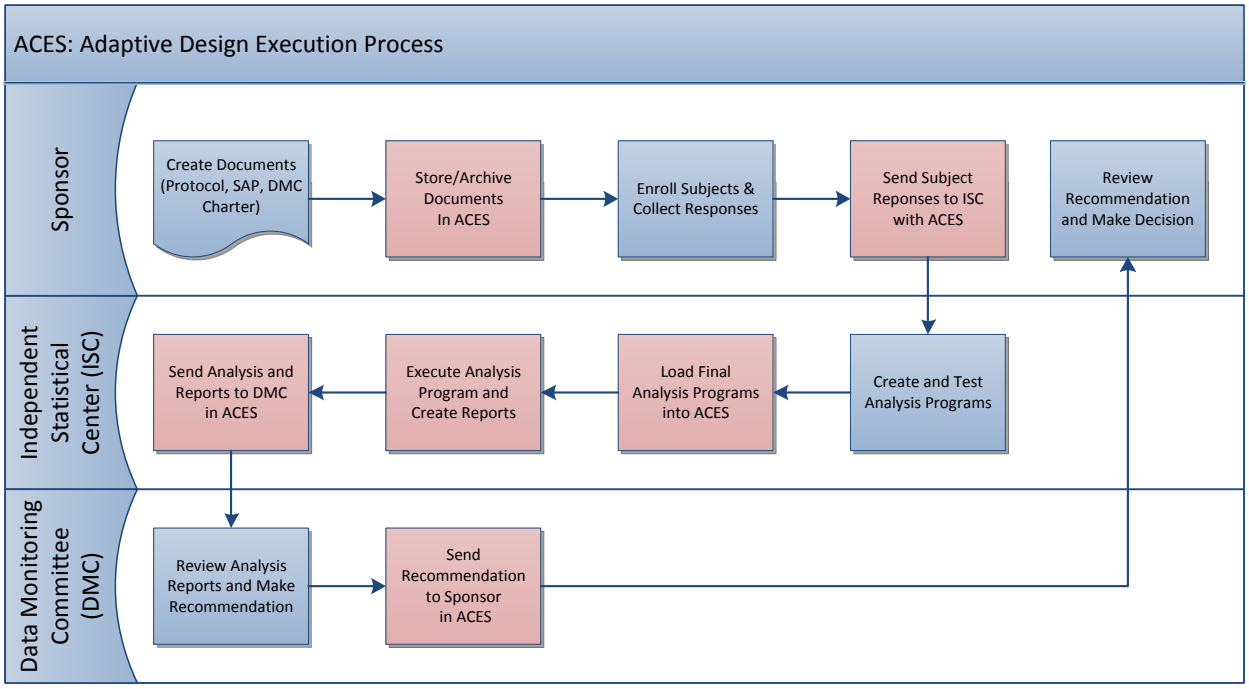
Please note: This recommendation is only intended as guideline for the DMC. The DMC is expected to also draw on their experience and incorporate their clinical judgement in making the final decision regarding Part B dose selection

Recommendations for sample size increase in Part B

Guidelines for sample size increases for Part B recommend sample size for dose W be increased by 150, sample size for dose X be increased by 150

The DMC reviewed the analysis report, supporting tables, listings, and graphs, and was able to make a recommendation to the trial sponsor. The recommendation was stored in ACES and notification sent to the sponsor representatives for review and acceptance.

The diagram below illustrates the process used during the interim analysis of the trial. Steps in red indicate where ACES was used to store and receive documents, and perform analysis of interim data.



Using ACES to facilitate the information sharing, analysis, and review between the ISC, DMC, and Sponsor ensured that all access to unblinded data was restricted to the ISC and DMC, and at no time did the sponsor have access to this information. The audit trail in ACES clearly documented 'who saw what and when.'

Innovative Technology

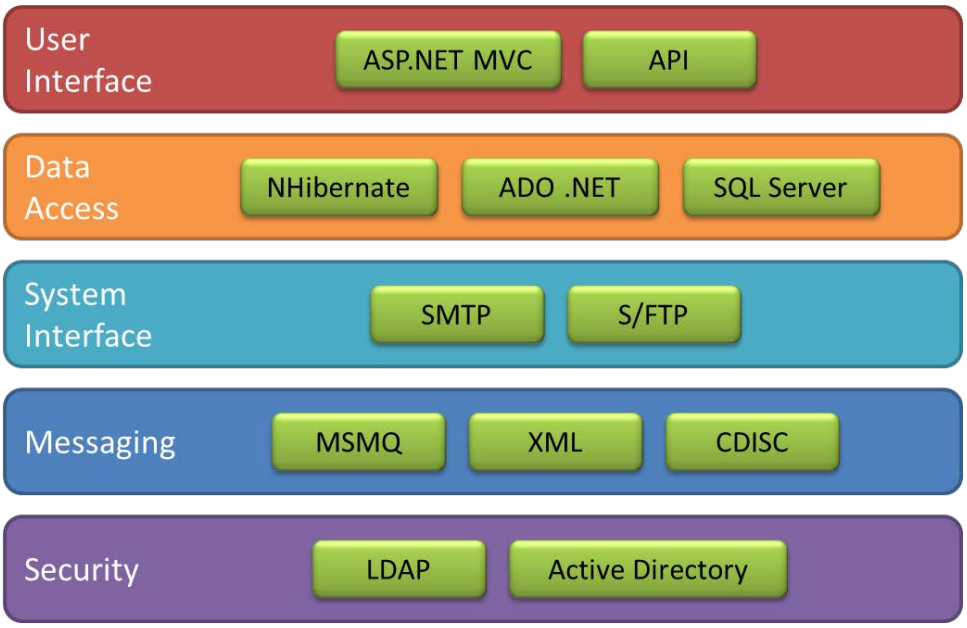
ACES has been designed to be the foundation platform that would evolve into suite of integrated applications, analytical utilities, and dynamic data dashboards that would help to optimize clinical trial operations, present data and information better, and allow stakeholders to make more informed decisions.

ACES has the capability to integrate with and leverage functionality from common enterprise infrastructure such as e-mail servers, databases, and security frameworks.

Built for the Enterprise

ACES has been built using standardized methodologies and technologies. This allows ACES and existing software and enterprise platforms to communicate using known standards instead of proprietary formats.

The figure below provides a high-level overview of the technologies and standards used and supported by ACES.

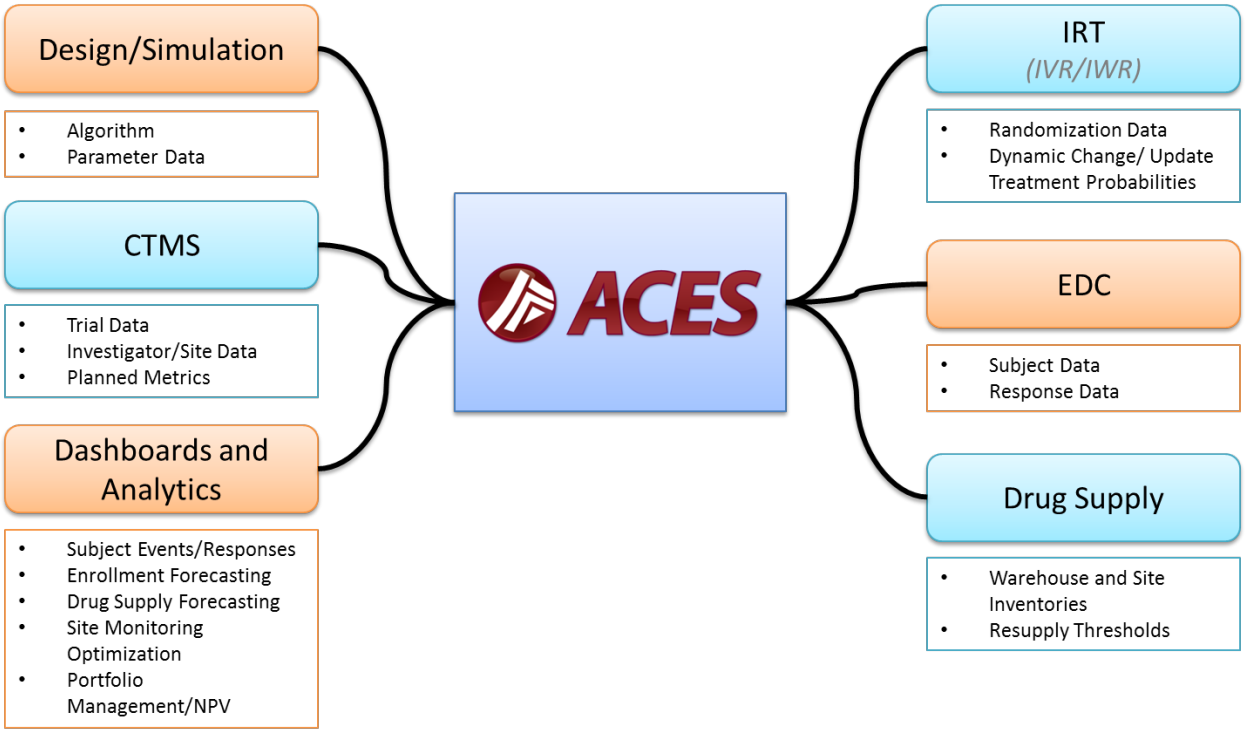


Integration and Extension

The ability to integrate and accept data from other systems (e.g., EDC, IRT, and CTMS) is critical for any clinical trials system. The heterogeneous portfolio of available software products combined with the business functions needed to efficiently and successfully conduct a clinical trial requires a system to be open and flexible to integration.

As a web-based application, ACES is able to integrate with other systems using standard protocols that are secure, encrypted, and do not expose the customer's internal network to unnecessary risk.

Integrating ACES with operational databases and data warehouses allows our customers to take full advantage of Cytel's innovative statistical analytics and reporting. ACES provides the customer with a dynamic and interactive view of the data. This allows the user to drill down into key data points without having to wade through countless tables and listings. The dynamic representation of safety and efficacy data expedites and enhances review by the DMC. Important data points can be given increased focus with the supporting data available just a few clicks away. No longer will hundreds of pages of tables, listings, and graphs be the only source of information required to support a DMC's decision during safety or efficacy review of data.



Software as a Service

Software as a Service (SaaS) is a method of providing software and its functions remotely as a hosted web-based application or service. This allows the client organization to access business functionality at a lower cost since the pricing is based upon usage. Also, because the software is hosted remotely by Cytel, the client won't need to invest in additional hardware and infrastructure, or worry about installation, upkeep, and maintenance. In addition, lower ownership costs, rapid time-to-benefit, easier scalability, and other substantial advantages make the SaaS model highly attractive to your organization.

ACES Hosted is a model of software deployment where Cytel licenses the ACES platform to customers for use over the internet. Our datacenter is located in the Boston, MA area and is SAS 70 Type II certified and PCI-DSS compliant.

The installation and qualification of ACES Hosted is performed and documented by Cytel; eliminating the need for the customer to spend additional time and resources.

By letting Cytel host ACES for you, the following benefits are immediately realized:

- **Accessible**
  - Ease of installation and distribution
  - Fully supported on all major operating systems and browsers, including Internet Explorer, Firefox, Chrome, and Safari
  - Seamless software upgrades performed when you want them with minimal or no downtime

- **Available**
  - Platform is always on
  - Instance configured and tailored to meet your requirements without the need for specialized customization
- **Scalable**
  - Operational and infrastructure resources are managed for a lower cost of ownership
  - Complete infrastructure is immediately available

Cytel – Science. Technology. Commitment.

The clinical development of medical drugs and devices is a crucial contribution to human welfare. At Cytel, we use science and technology to change the manner in which clinical trials are designed and conducted because we know that is the way to improve success rates.

We provide unrivalled biostatistics and operations research knowledge to our customers. Our knowledge is available in the form of both software and services. This knowledge, supported by our capabilities in trial simulation, statistical programming, data management, and medical writing is what makes us different.

All of our customers believe this once they have worked with us.

Our Science

We apply advanced biostatistics knowledge to get the trial design right – selecting the right endpoints, the right population, the right data collections and monitoring strategy, the right form of adaptation (including none), and the right interim decision rules.

We apply the rigorous, quantitative methods of operations research to solve problems in the conduct of clinical trials, such as forecasting enrollment, forecasting events when they are the endpoint, and optimizing medical supply to avoid large, costly waste due to overage.

Our Technology

We define technology as the 'know-how' experts use to achieve certain results consistently and embodying that know-how in tools and processes for others to reliably get correct results. Our technology takes the form or software and simulation tools:

- Statistical Analysis
  - StatXact
  - LogXact
- Statistical Design
  - East
  - Compass
  - SiZ
- Trial Monitoring
  - ACES
- Adaptive Design Simulation
- Clinical Supply Modeling and Management
- Event Forecasting
- Enrollment Forecasting
- Randomization
- SAS Productivity Tools
- Medical Coding
- CDISC Migration

Our Commitment

We are committed to excellence in implementation, with an emphasis on obtaining the best information to enable good decisions.

We are committed to working collaboratively with our clients. Our clients come to Cytel because they want our best advice and not just follow orders.

We work best with those who want to innovate in clinical development in order to improve success rates.

Our Experience

Cytel is a leading provider of clinical research services and trial design and analysis software primarily for the biopharmaceutical, medical device, academic and government research markets.

Cytel has designed and defended more adaptive trials for sponsors than any other service provider. These innovative trials have helped pharmaceutical, biotech and device companies increase their clinical success rates while reducing development time and costs.

Our experts have mastered the statistical methodologies of adaptive trials and regularly train industry and FDA biostatisticians in the latest adaptive trial designs. All methods employed are published, acceptable to regulators, and validated in practice.

47 of the top 50 pharmaceutical companies use our software.

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