

entimICE[®] DARE

An integrated, controlled and full GCP compliant environment that provides the clinical data transformation, analysis and reporting that pharmaceutical research organizations need in accelerating drug development.

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Abstract

The processes that lead from the discovery of a substance to the approval of a drug are time consuming, cost-intensive and risky. To bring a new drug to market can take anywhere between 10-15 years with average R&D costs of 800 million US dollars. The available time for return on investment can be very short because patents are granted for only 20 years and the patent clock starts ticking early on, when the drug is submitted for investigation.

For pharmaceutical companies time is the key factor to innovation. The industry has identified the following main goals:

- increase the quality and speed of summary information available for decision points
- automate and facilitate company validation efforts
- increase drug development knowledge by integrating multiple company data sources
- reduce costs associated with analyzing and preparing the data for regulatory submission.

IT systems play a significant role in supporting and optimizing the business processes of pharmaceutical research and development.

Currently, there are a number of tools and applications on the market that are used for varying purposes. The systems, however, don't share an interface, making it difficult to get cross-system integrated information. This problem is often addressed by many one-on-one links between the various systems, which result in considerable maintenance, validation efforts and version dependencies. To develop data transformation and reporting programs, files are typically copied from a file system and then edited, managing the testing cycle is a major challenge in such an environment.

Pharmaceutical companies require an environment where data can be loaded by end users from a variety of sources (CDMS, SAS, etc.), where programs and reports can be built from a library of reusable standards, and all authorized users can easily access the data they require.

entimICE DARE provides a comprehensive and flexible solution to the present situation while anticipating ever increasing demands on quality and safety. entimICE DARE is the entimo Integrated Clinical Environment for Data Analysis and REporting. The product seamlessly connects the different stages in clinical development. It enables the user to view, transform, analyze and report data across clinical applications, projects or trials within the same application. Regulatory reports can be easily generated and offer more transparency and flexibility than compliance currently requires, due to sophisticated audit trail functions, traceability, version and safety controls.

The system includes tools to define data structures, load or access data from a variety of sources, define and run SAS programs for transformation, analyzing and reporting any configuration of data, and produce formal and ad-hoc reports.

entimICE DARE also integrates DBMS applications as well as the customers' custom software systems in a complete analysis and reporting environment by unifying their meta-data in a repository and by offering controlled activation of functions from these applications.

entimICE DARE implements the latest CDISC clinical data interchange standards for data management and submission (ODM and SDTM) and is fully conformant to the FDA 21 CFR Part 11 and ICH GCP requirements and regulations.

Fundamentals

Pharmaceutical and biotechnology companies are currently faced with a research and development machine that is becoming increasingly expensive and difficult to maintain. More and more patients are taking part in an increasing number of long-term clinical studies while drugs are targeting more and more complex diseases. Every year, more than 8800 new clinical studies are initiated. New developments in science and technology, such as genomics and high-throughput screening, are responsible for introducing more potential drug targets to the development pipeline.

The risk of failure is very high, because the researchers in the field of drug development are pioneers in their field. Out of 10,000 substances, only 20 reach the pre-clinical phase and only 1 eventually becomes an approved drug.

The cost of developing a new drug and bringing it to market now averages \$800 million dollars and can take anywhere from 10 to 15 years. A patent, however, is granted for only 20 years from the time the Investigational New Drug (IND) is submitted. Once the patent has expired, generic drugs typically flood the market, significantly curbing profits. The time available for return on investment is therefore very short.

Pharmaceutical companies try to minimize the risks involved in the failure of individual drugs by expanding their product portfolios. The rising costs in R&D, however, mean that fewer and fewer drugs ever enjoy financial success.

There are two principal ways of increasing profitability, reduction of expenditures, on the one hand, and the time it takes from laboratory research to new drug approval. At the same time quality has to be maintained in increasingly complex environments.

Due to increasing safety and quality requirements, the regulatory authorities are becoming more and more restrictive in order to protect the consumer. Today, knowledge of the effects and combined effects of drugs and the needs of specific patient groups is steadily improving.

To make the drug approval process more efficient and manageable, the FDA has now put a

requirement in effect that data and documentation be provided in electronic form. This requirement is being implemented at this point but processes are still in a transition phase.

In view of regulatory authorities' increasing scrutiny regarding the quality and traceability of the submitted data, it is essential that IT procedures and systems guarantee the authenticity and accuracy of the data which they have helped to record, check, manage, analyze and report on during clinical trials. It must be apparent which program recorded, checked, managed, reported or analyzed which data. And it must be transparent which user modified which data and when. In addition, it must be certain that the user had the authority to carry out this task. Misuse must be prevented (21 CFR Part 11).

Data Analysis and Reporting in Pharmaceutical Clinical Development

Currently there are a number of tools that support various aspects of the research process, such as trial design, data entry, source document tracking, data cleaning, analysis and reporting.

In such a heterogenous environment it is difficult to get cross-system integrated information. This problem is often addressed by many one-on-one links between various systems. As a result, maintenance is considerable and validation cumbersome. Version dependencies are another problem.

Data managers, statisticians and programmers typically develop data transformation and reporting programs by copying files from a file system and then editing the copied files. However, the integration of data across systems is time-consuming. Because data is dispersed, end users oftentimes cannot access crucial information without the involvement of a technically skilled person. Delays during regulatory submission preparation, though, can be very expensive.

At this point pharmaceutical companies utilize their clinical data management system of choice (ClinTrial, Oracle Clinical, etc.) to perform clinical data management functions such as collecting, cleaning and maintaining data and meta-data from clinical trials. Data in clinical data management systems are depicted in a relational structure, which allows flexible study setup and data entry but does not implicitly support reporting. Clinical data management systems (CDMS) are designed to handle data from clinical trials, they are not optimized for handling cross-trial data and to perform sophisticated data transformations required for statistical analysis.

For these reasons, a separate system, normally SAS is used for the analyses of both trial and cross-trial data. The results and reports are collated in a document management system and then published.

The regulatory authorities require that more and more steps of the submission process need to be controlled and traceable. Data modifications

(e.g. the fact that data was changed) need to leave audit trails.

The analysis and reporting of data collected in clinical trials must be controlled and must deliver reproducible results. Special emphasis has to be paid to a controlled environment that complies with 21 CFR Part 11.

The conclusion for pharmaceutical companies is a solution where data can be loaded by end users from a variety of sources (CDMS, SAS, etc.), where programs and reports can be built from a library of reusable standards, and all authorized users can easily access the data they require. Automation of processes whenever possible would be a great extra benefit.

The Solution: entimICE® DARE - The entimo Integrated Clinical Environment for Data Analysis and REporting

entimICE DARE is an integrated and controlled environment for clinical data analysis and reporting in clinical development. It is a comprehensive and flexible product that ensures seamless operation across different stages of clinical development. entimICE DARE enables the user to view, transform, analyze and report data across clinical applications, and across projects or trials, within the same application, and in a regulatory compliant manner. It provides a unified, reusable and compliant production environment for managing clinical information and producing regulatory reports.

At the heart of the solution is a so-called repository, in which all of the information about data is stored, including component modules and data necessary to guarantee the system's functionality and navigation through its various component modules.

The system includes tools to define data structures and load or access data from a variety of sources. It defines and runs user SAS programs for transformation. It analyzes and reports any configuration of data, and produces formal and ad-hoc reports. It gives the user the ability to recreate data and reports as they existed at any point in time.

Any data modification activity initiated within the system can be configured in such a way that it leaves a trail in the repository or in the various accessed databases. Audit Trail, Version Management and Historization are basic system functions. This approach allows a high level of transparency and clarity regarding data contents and cross-referencing.

entimICE DARE allows for maximum adaptability. The environment is so open and extendable that new as well as modified applications can be integrated very easily. It is usually enough to change configurations instead of code. The system's modular architecture facilitates a high degree of transparency and accountability related to software development, thus simplifying continuous, controlled modification and upgrades.

entimICE DARE integrates Data Base Management Systems (DBMS) applications as well as the customers' custom software systems. DARE is a complete analysis and reporting environment that is able to unify meta-data in a repository and by offering controlled activation of functions from these applications.

entimICE DARE manages and maintains meta-data via individual process components such as files, programs and outputs in a repository, or in any combinations of these. It therefore maintains up-to-date knowledge of the processes. Partial processes can be automatically activated and operated, according to preset rules.

By means of process monitoring, interface reduction, data knowledge and corresponding plausibility controls entimICE DARE guarantees better data quality, information updates and traceability. This not only leads to an improved database but considerably speeds up the access to information through the use of reports, analysis and queries.

entimICE DARE implements the latest CDISC clinical data interchange standards for data management and submission (ODM and SDTM) and is fully conformant to the FDA 21 CFR Part 11 and ICH GCP requirements and regulations.

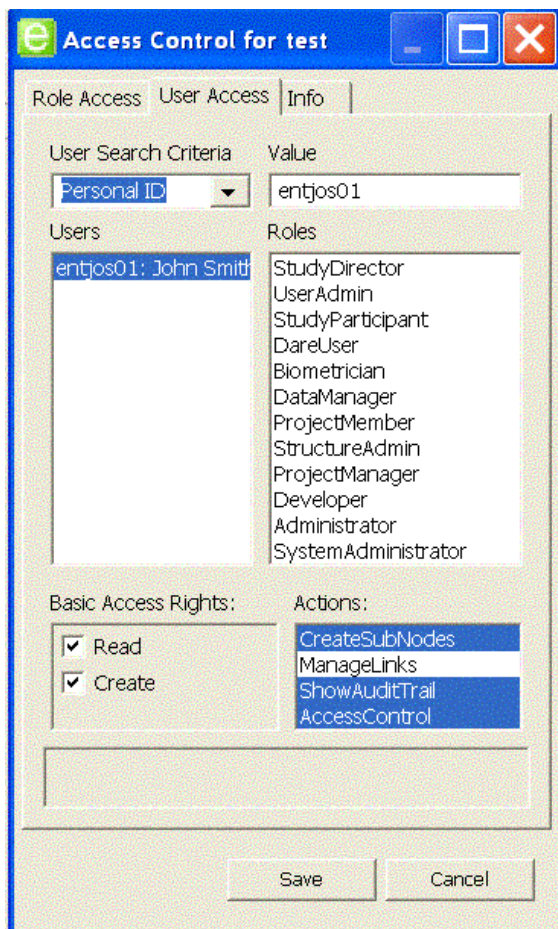
entimICE® DARE: Functional Description

entimICE DARE provides an Integrated Clinical Environment (ICE) for Data Analysis and Reporting. Its complex functionality and adaptability makes it the only product of its kind on the market.

User Groups and Access Privileges

There are essentially two types of user groups:

- Clinical research personnel (clinical monitors, clinical research associates) who can read and review data within and across trials and are able to run pre-defined reports.
- Data managers, statisticians and programmers, who can develop analysis and reporting programs, in addition to the above.

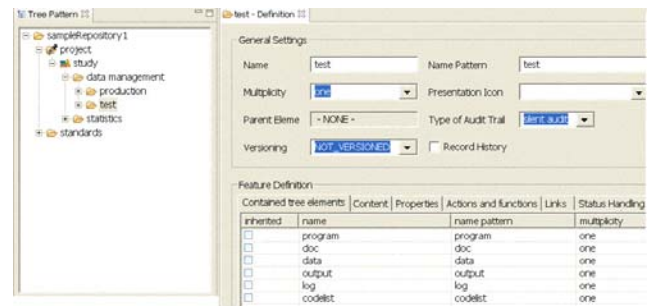


In entimICE DARE, roles and privileges are defined through users, user roles and user groups. Users are assigned to as many groups and

group roles as appropriate. These groups are then assigned to security classifications. Objects are also given security classifications for the various operations allowed for them. Only if the user has the correct role on a group that has matching security classification, is he allowed to perform that operation.

Hierarchy and Navigation

The hierarchy and classification of the various objects and their relationships are defined during a customizing phase. This is necessary since hierarchy requirements are different from company to company and even from study to study. Customization within the flexible structure of entimICE DARE allows for maximum adaptability.



Navigation is based upon the hierarchy of the arranged objects and their relationships to each other. Functions on objects are assigned on the basis of user access rights and other predefined rules. As a result the Graphical User Interface (GUI) displays only the parts of the navigational tree that are applicable to the user's access level.

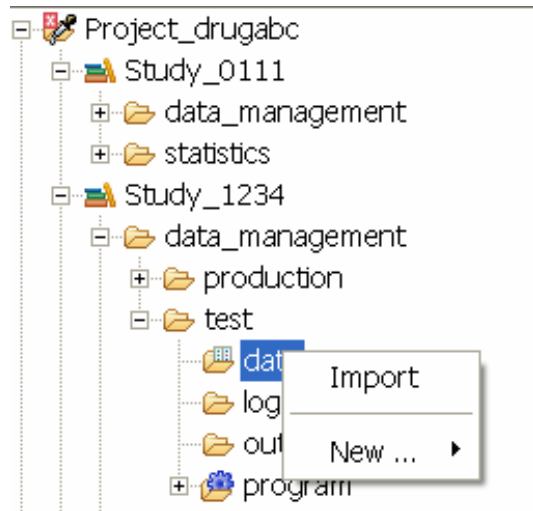
Clinical Data Loading

To enable clinical data reporting in entimICE DARE, the clinical data first has to be imported from external source systems. Data loading is handled through adapters. entimICE DARE provides adapters for CDMS meta-data, database tables (Oracle, DB2), SAS datasets / catalogs / transport files, ASCII files (CSV, TXT, Excel) and XML files (e.g. CDISC ODM). Data can also be loaded incrementally, if the source system supports it. Data loading may be accomplished by copying data into the system or just pointing to the location where the data is stored.

There are two components to loading data: The actual data source supplying data to the system

and the meta-data that describes the structure of the data to be loaded.

For data from the CDMS system and SAS, the meta-data is supplied directly from the source system to entimICE DARE via the adapter. The CDMS adapter supports the loading of meta-data from a CDMS global library. The study data is loaded using CDMS SAS data extract views including CDMS meta-data. SAS datasets (for example, those received from CROs) are loaded by entimICE DARE's SAS adapter.



After loading clinical data and meta-data, into the system, the data can be further processed and transformed within entimICE DARE to prepare analysis data sets, to perform data building for reporting or to combine them across trials to build a project database.

In entimICE DARE programs can be created to transform, analyze and report data. The Graphical User Interface (GUI) allows users to write program logic (i.e. source code) within its framework and to save source code files for reuse. For maximum adaptability, external reporting tools can be integrated into entimICE DARE as well.

Clinical Data Transformation

Data transformation in entimICE DARE refers to programs designed to transform loaded data or output data from another data transformation into a structure that can be used for reporting.

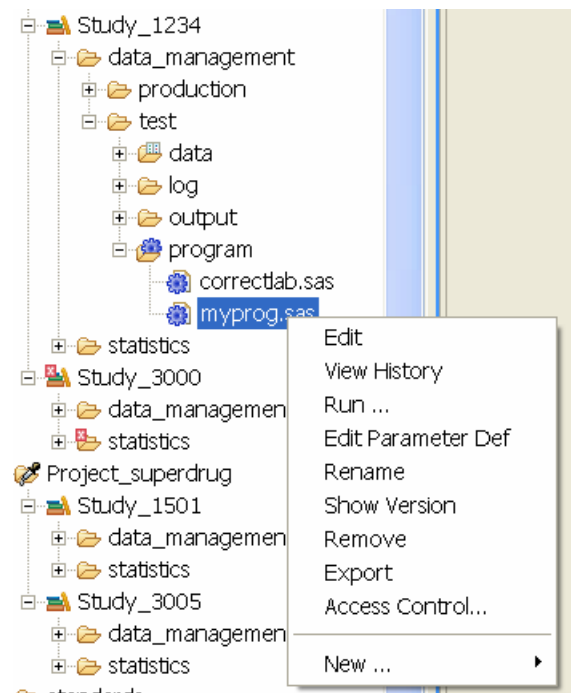
The data transformation programs are also used to create new derived variables and analysis data sets.

The program logic for data transformation is developed in the corresponding IDE (e.g. SAS) as mentioned earlier. Data from trials can be combined to create project databases using programs developed in the SAS IDE.

Once the data transformations are defined, they can be executed on demand.

Clinical Data Analysis and Reporting

Programs for analyzing and reporting clinical data are developed in the SAS IDE, much in the same way as programs for data transformation.



An export of objects (metadata, data, codelists, programs, format catalogs, outputs, logs) out of entimICE DARE is possible to all available file structures accessible by the user depending on his access rights.

The physical formats of export can be SAS (data sets, catalogs, transport files), ASCII files (SAS, TXT, LOG), RTF files, PDF files, HTML files, and XML structures (esp. CDISC ODM, SDTM).

About entimo®

entimo is a provider of innovative eR&D products and professional services to the pharmaceutical and agrochemical industries. entimo is also an established supplier of quality IT solutions to the European regulatory authorities. entimo's dedicated staff of software professionals has developed and maintained several custom solutions (such as CDMS, LIMS, clinical portals, etc.) for large pharmaceutical and crop science companies as well as for regulatory authorities. Bayer HealthCare AG, Bayer CropSciences AG, Schering AG, Boehringer Ingelheim Pharma GmbH & Co. KG, Altana Pharma AG and BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) are just some of our customers that have established and maintained a long term relationship with us. entimo AG is a privately held company with headquarters in Berlin, Germany.

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