Electronic Data Capture in clinical trials– interface design and evaluation and system validation

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Abstract: *The objective of this project was to develop an interface for a tailored EDC system to be used in a bioavailability clinical trial, to benchmark the EDC process and to develop a validation protocol that could be applied to a currently active pharmacovigilance system.*
A database structure that can host multiple clinical trials was created and an interface to access it was implemented. A three tier architecture was used and a thin client web interface was chosen to access the database. A validation plan was developed taking in consideration the pharmacovigilance database's risk and requirements. Nine test cases were created and executed as part of a test plan to assess the overall validated state of the system.
Paper based transcription errors' rate was 1.2/1000 (double data entry) and 5.91/1000 (single data entry). EDC eliminated this step and therefore transcription errors. The number of queries dropped 58.4% when using EDC and they were resolved 17.5 times faster, while the time from beginning of the project until database lock increased from 89.5 days to 185 ± 16.3 days. The time from last clinical procedure to database lock decreased 38% using EDC.
There was an overall gain in every performance and quality benchmark conducted in the EDC test, except in the total project time. EDC systems should be designed so that database and interface modifications are minimal on subsequent clinical trial projects.
Seven of the nine test cases were successful. The pharmacovigilance system database was validated and suggestions were made in order to train users to operate with the system and overcome its weaknesses.

Keywords: EDC, clinical trials, validation, benchmarking

Introduction

In the “critical path” (pre-clinical and clinical trials' phase) of drug development, data management is estimated to represent 30% of the total cost of the process [1]. Data collected in clinical trials is the determinant factor to determine drug safety and efficacy. During clinical development data must be collected and analysed before it is sent to the regulatory authority in the form of a clinical (or nonclinical) report form. The ICH has issued a guideline for the structure and contents of clinical report forms [2]. The regulatory pathway in Europe may not always coincide with that observed in the US, however, the general flow of information and data generation is largely similar.

Data from participants is collected individually in *Case Report Forms (CRF)*. The ICH defines a

CRF as *a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject* [3]. The CRF is defined in the clinical protocol of the trial and data can be inserted directly into the CRF or copied from another source document. Source documents are, according to the ICH, original documents, data, and records.

The typical process of data capturing in clinical trials is paper-based - the percentage of trials conducted using paper was 85-90% [4] in 2003. The remaining trials used an electronic data capture (EDC) process where, instead of using a paper CRF, an electronic case report form (eCRF) is used and data is introduced directly into an electronic system.

In a study published in 1992 transcription error rate was estimated to be 22/1000 fields in a single data entry and 15/1000 fields in a double data entry process [5]. Another study about transcription error rates refers values between 10.4 and 13.1 per 1000 fields for single data entry and between 2.0 and 2.8 for double data entry processes [6]. The double data entry process is therefore the gold standard in the paper-based method. An EDC edit check system is estimated to reduce errors by 70% [7].

In 1997 the FDA issued the CFR Part 11 (Code of Federal Regulations 21, Part 11). This document is aimed at regulating electronic records, electronic signatures and electronic submissions. In particular, the Part 11 defines the conditions under which electronic records and signatures are equivalent to paper records and handwritten signatures executed on papers [8]. In addition to the CFR Part 11, the FDA issued a Guidance for Industry in 2003 entitled *Part 11, Electronic Records; Electronic signatures – scope and application.* This guidance clarifies which records need to comply with Part 11. If records must be maintained due to predicate rule requirements, then electronic records that replace them must comply with Part 11 [9]. Part 11 also requires the use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Previously recorded information cannot be obscured by the new changes [8].

In 1999, the FDA issued guidance for the industry on *Computerized systems used in clinical trials ,* where it warns to the necessity for clinical trial sponsors to ensure and document that computerized systems conform to their requirements for completeness, accuracy, reliability and consistent and intended performance [10]. Documentation should provide an overall description of the system and the relationship of hardware, software and physical environment.

The type of validation effort depends, among other factors, on the type of software. The guidance notes that, in the case of off-the-shelf software (i.e., an already finished software purchased from a third party vendor), most of the validation should already be done by the company that wrote the software. In this case, the sponsor should have documentation (provided by the vendor) of the design-level validation and should limit validation to functional testing. In 2002, a final guidance for industry and FDA staff entitled "General Principles of Software Validation" was issued. The document serves as guideline for the validation of medical devices software or software used to design, develop or manufacture medical devices. In this document, software validation is defined as *"confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled"* [11].

In September 2007, the PIC/S published a revision of its *"Good practices for computerized systems in regulated GxP environments"* guidance [12]. These rules and guidelines clearly define the necessity of validating all computerized systems used in regulated environments, which includes the validation of all software used in clinical research and pharmacovigilance applications. The PIC/S defines validation as *a system that assures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of software and system development, its*

implementation, qualification and acceptance, operation, modification, qualification, maintenance and retirement .

Methods

Requirements elicitation

The design of an eCRF should be as similar as possible to the paper CRF to relieve the burden of process change and to prevent the introduction of external variables when comparing the two systems. The EDC system had to comply with FDA's requirements, namely with CFR 21 Part 11.

The system's electronic signature was implemented with a username login and a password. Information could not be available to anonymous users but only after successful log-in and some sort of identification (such as username or the person's name) must be visible at all times. In addition, users could log off when leaving their workstations.

An audit trail was a functional requirement of the system and no information can be deleted from it to comply with Section 11.10 (e) of Part 11. This time-stamped audit trail independently records the date and time of operator entries and actions that create, modify or delete electronic records. The record changes cannot obscure previously recorded information and must be retained for a period at least as long as that required for the subject electronic records.

The system should allow authorized users to determine database lock to prevent further data changes. Database lock is performed when the clinical trial ends and all data has been collected. Only the project manager shall have permissions to perform this task. After database lock, every necessary database unlock date should be recorded and special clearance was needed to perform this action.

Regarding the interface, each subject's CRF cannot be locked until every field has been filled out. Ideally, no visit should be concluded without this requisite. In parallel, the user must always be aware of the system's state regarding data entry. In particular, the user must know which fields are already filled out and the value that is currently entered.

Investigators in Area d'Investigació Farmacologica Clinica do Hospital de Santa Creu i San Pau (AIF-HSCSP) located in Barcelona and sponsor users in Lisbon needed to be able to quickly access information. A query system must be in place so that the monitor can perform his tasks.

Table 1: System's functional requirements

Requirement	Category
Electronic signature shall be composed of a username and a password	1
Users must log-in with their electronic signatures to access information	1
User roles shall exist with different privileges	1
Audit trail with signature and date on every data modification	1
Data from audit trail cannot be deleted	1
Database can be locked by users with sufficient privileges	1
eCRF cannot be closed until all information has been entered	1
Data must be readily accessible to system users in different locations	1
Export data to allow further manipulation	1
User information always visible	2
Edit checks shall be present to improve data quality	2
Query system shall be available to enable complete e-monitoring	2
Automatically import lab results	2

Data interoperability should also exist both in input and output perspectives. Laboratory results regarding plasmatic concentrations are exchanged in Excel format and an automatic import system was required. All information from the clinical trial should be able to be exported to a data format that enables further data manipulation, such as XML, Microsoft Excel, or SPSS (SPSS Inc.) and SAS (SAS Institute Inc.) compatible files.

Edit checks can prevent users from entering wrong or illogical data or simply forgetting to enter some data.

Table 1 lists the functional requirements of the system that have been discussed. A category is also attributed to each of the requirements to distinguish essential requirements (1) from highly desirable requirements (2) [13].

System analysis and design

A three-tier architecture was used in the EDC system (Figure 1). Microsoft's ASP.Net framework was chosen to develop the interface prototype (top and middle sections in Figure 1) and MS SQL Server 2005 was chosen as the DBMS (lowest part in Figure 1). The server was built in a Windows XP running Internet Information Services (IIS), and SQL Server 2005.

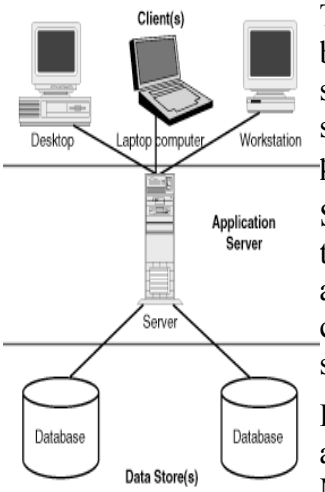

Figure 1: Three-tier architecture proposed

The EDC was used in a cross-over, open-label, randomized, bioavailability clinical trial with two treatment periods during which a single oral dose of each treatment was administered; periods were separated by a minimum washout period of 14 days. These periods were preceded by a screening period and followed by a final control period.

Six different actors were implemented: the anonymous user, the monitor, the investigator, the data manager, the project manager and the system administrator. Each of the roles had different access to the seventeen use cases identified in the eCRF. The permissions given to each actor in the system are summarized in Table 2.

Four different user roles were created using ASP.NET's authentication and authorization framework, based on these actors. The Project Manager and Data Manager roles were merged in the same interface role (Project Manager). Anonymous users were denied access to the entire application and redirected to a login page.

Table 2: Actors and use cases' permissions

	Investigator	Monitor	Data manager	Project Manager	System administrator
Access validation	X	X	X	X	X
Add subjects to the trial	X				
Automatic Edit Checks (performed by the system)			Not applicable		
Clinical trial data lock				X	
Clinical trial unlock				X	
Create user accounts					X
Data entry and data changes in the eCRF	X	X			
Database administration					X
Drug concentration data management			X	X	
Insert source documents	X	X			
eCRF Lock	X	X			
eCRF Unlock				X	
Query answer	X				
Query issuing		X	X		
Subject exclusion	X				
Trial data export (including audit trail export)			X	X	
View eCRF data	X	X	X	X	X

Object design and implementation

The eCRF interface was composed of four layers: the login layer, the clinical trial layer, the subject's eCRF layer and the event layer. Vertical navigation along the pages follows this order.

Figure 2 exemplifies the four layers navigation while performing a task (Use Case: data entry by an investigator). After successfully authentication in the system, the clinical trial is selected; the system sends the user to the clinical trial layer, where information and actions regarding the clinical trial can be accessed. When choosing a subject from the clinical trial's volunteer list, the user is taken to that subject's eCRF, therefore entering the eCRF layer. After selecting a period (e.g.: Screening) and a specific task (e.g.: Demographics), the user is sent to the specific task's layer, where he can enter data. When the user has finished using the system he logs out and is sent back to the login layer.

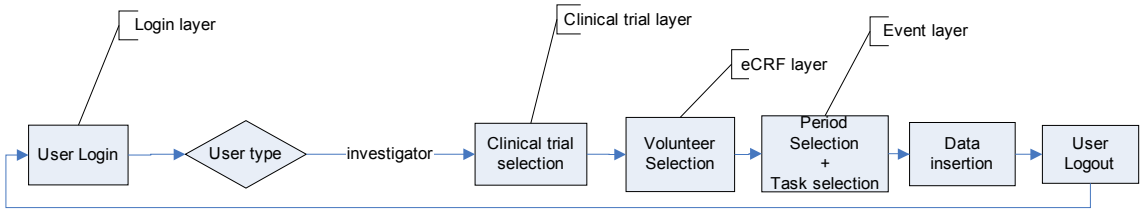

Figure 2: Navigating through the different interface layers

This layer notation also indicates a certain hierarchy in the components of the interface: a clinical trial is composed of eCRFs, which in turn are composed of periods that are formed by events.

Interface layout

The interface was composed of three main areas (Figure 3). In the map bar the user had information about the current session state, including the current clinical trial, the subject, the period and the event that is currently selected. Buttons to save data or undo changes, as well as quick "next" and "previous" buttons are also located in the map bar. In the left frame users could log-in to the system. After successfully authentication, the navigation frame showed the username of the user currently active. The navigational frame was dynamic and contents depended on the layer that the user is currently in. In the working area the actual eCRF data was viewed, entered and corrected, and all the clinical trial related tasks were performed – query management, source document management and trial administrative options.

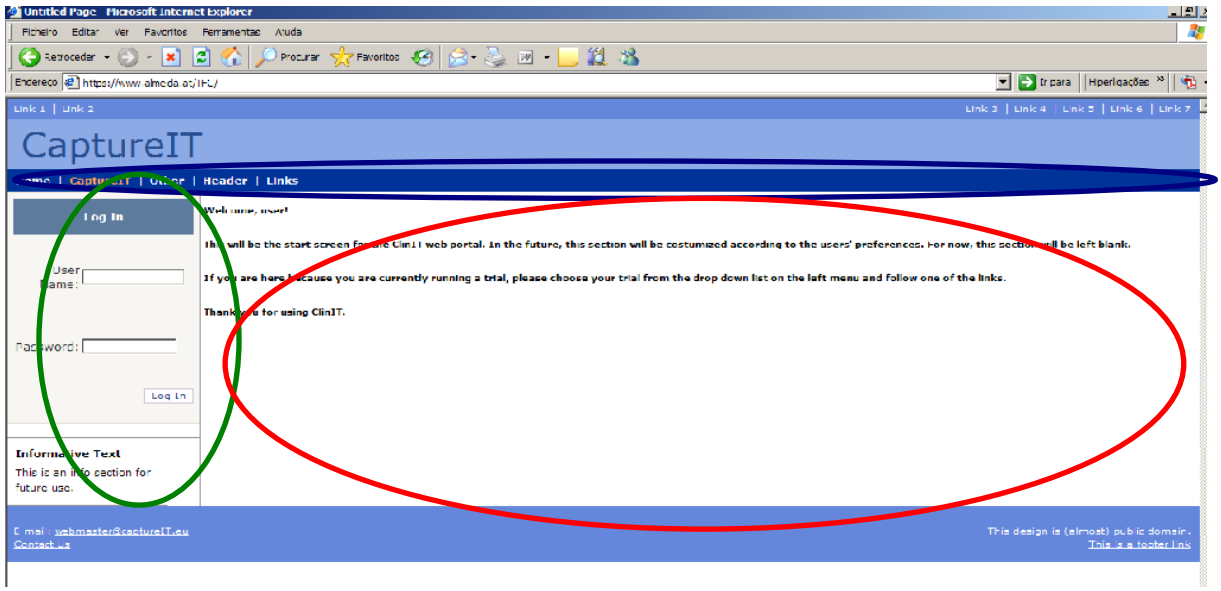

Figure 3: eCRF areas - Map Bar, Left Frame (navigation), Working Area.

The eCRF interface's edit checks were composed of a colour warning and a text warning. Whenever the specific data entered did not pass the edit check's criteria, the value in question was highlighted in a red box so that users quickly saw there is a problem with the inserted data, and a warning message written in dark red informed the user about the reason for that edit check. Table 3 lists the

different types of edit checks available in the interface.

Table 3: Interface's edit checks

Type	Description	Example
Logical	Prevents users from inserting values that do not make sense for that data type	Inserting text in the "age" field or a number in a date field
Criteria violation	Warns the user to a possible violation in the Inclusion or Exclusion Criteria	Age > 18 years, positive value in the virus screening test for HIV
Filling rules warning	Prevents users from not complying with the harmonization rules defined for data entry	The decimal separator is "." (e.g., 0.2); dates are written in the dd/MM/yyyy format
Required field	Eliminates the possibility of fields being left blank	No field can be left blank in the eCRF

E-Monitoring

An e-monitoring system was created on the top section of the working area of each eCRF event to allow users with monitor privileges to monitor eCRF pages as soon as they are filled.
The query system implemented categorized a query into one of three states: Sent (after a query was issued by the monitor), Answered (once it was answered by the investigator) and Solved (after the monitor read the answer and informed the system about what measures were taken given that specific answer). The query process is described in Figure 4.

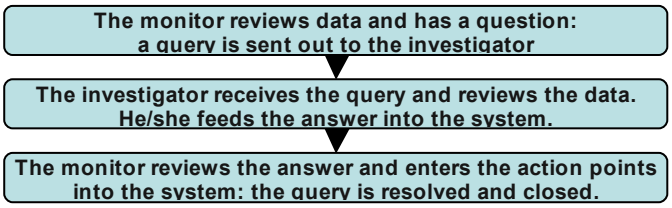

Figure 4: Process diagram for query management

Performance indicators

To compare the paper-based model with the prototype EDC process the total project time was organized in three periods: pre-trial, clinical trial and post trial. Pre-trial comprises all tasks necessary to create the data collection medium (CRF and eCRF). Activities that are common to both processes, such as protocol development or regulating authorities' and ethic committee's approvals, are not considered in the benchmarking. Clinical trial period is the same for both processes. During this period data is entered in the CRF/eCRF. In the post trial period data is reviewed, queries are managed and database is locked. Double data entry was considered for the paper process, as it currently is reckoned as the industry's gold standard. Three performance indicators were measured (Table 4). Historical data from a previous multi-center study conducted by DMED/GT was used to calculate the average response time in the paper based process [14].

Table 4: Performance Indicators

Indicator	Measurement
Time between the beginning and end of the project	The sum of the three periods mentioned
Time between last clinical procedure and database lock	Time between last clinical procedure and database lock is the interval between the end of the clinical trial and post trial periods.
Average response time	The time that is necessary to resolve a query, i.e. the time elapsed between the date the query is sent and the date the query is received back by the monitor after it has been answered.

Quality indicators

Two online questionnaires were conducted. Both questionnaires used a 7 point Likert scale. The first questionnaire was aimed at measuring the perceived usefulness and ease of use of the system. To measure these two variables, users received *in loco* training sessions to learn how to operate the

interface. After the training session, users were asked to answer a 15 question online questionnaire aimed at characterizing users on their prior experience with computers and EDC systems, evaluating users' perceived usefulness and perceived ease of use of the system.

The second questionnaire was conducted after the clinical trial ended and users worked with the system extensively. It was aimed at determining user satisfaction with the interface created for the EDC prototype. A Generic User Interface Questionnaire (QUIS) was used [15], consisting of 27 questions that asked users to evaluate the interface on five sets of characteristics: overall reaction to the system; screen; terminology and system information; learning; system capabilities.

The transcription error rate and number of queries were also measured. The transcription error rate is the measure of the frequency of data errors between the source documents and the database where information is stored that are attributable to human errors in the transcription process. In the paper process with a double data entry system, operators can make transcription errors. In the EDC process, because data is entered directly in the database, the transcription error rate is equal to zero. The total number of queries is calculated when the data reviewing process is completed.

To evaluate both the transcription error rate and the number of queries issued in the paper-based process, a sample of the CRF was chosen by experienced industry professionals and data from that sample was transcribed by two users independently. This sample consisted of a total of 1692 fields (69% of the complete CRF). The sample is assumed to be representative of the complete CRF. The transcript data was then crossed checked against the source documents to retrieve the transcript errors. Afterwards, double entered data was crossed checked to build the final database. This final database was compared again with the source documents to find if any error subsisted in the database.

Validation

A validation plan was created for a Pharmacovigilance Database with the contents shown in Table 5. The database's system requirements were created as the first step towards the validation process, and a risk assessment was performed.

Table 5: General contents of the Validation Plan

Contents	Description
Version Control and Plan Approval	A list of the document's versions and the identification of the qualified staff that approved it
Objectives	Brief description of the objectives of the validation plan
System Description	General description of the system being validated, including reference to the system's requirements
Risk assessment	An explanation of how risk was assessed for the software and a list of potential risk issues related with system usage
Scope	Constraints on the validation activities, assumptions made for successful execution of the Validation Plan. Definition of the boundaries to the validation activities and exclusions within the scope
Tasks and responsibilities	List of the tasks that will be performed and identification of the person(s) responsible for each task.
Validation maintenance	Explanation of how the validated state will be maintained thereafter.
References	List of all the documents referenced in the plan

Nine test plans were written covering all the database's functions and requirements. A traceability matrix (visible in Table 6) made the correspondence between the validation activities and the requirements covered by them.

Table 6 - Validation tests

Task	Description	Test plan	Requirement #
Error frequency	Determine the weighted error frequency of the AEs in the database	Test Case 9	4
Retrospective missing values frequency	Determine the missing values' frequency in the database	Test Case 8	5
Function: Save	Assess the Save function of the software, in normal conditions and using stressful values	Test Case 1 Test Case 5	1
Function: Edit	Evaluate the Edit function of the software	Test Case 2	1
Function: Query	Evaluate the query functionalities of the software	Test Case 3	2,6
Function: Report	Evaluate the software's capacity to export the data	Test Case 4	7
Security: backup	Determine the backup procedure in place for the system	Test Case 6	8
Security: access control	Evaluate how the system handles authorization to access the database	Test Case 7	3,9

Results

Performance indicators

Clinical trial activities were considered the same for both systems and lasted a total of 37 days. The estimated number of working days that were necessary to build the system was 163 ± 16.3 days. Because the prototype's development continued beyond the clinical trial's beginning date, there was an overlap between the system's development and the clinical phase. The actual time between the beginning and end of the project was 163 days for development plus 22 non overlapping days until database was ready for closure. The last query was resolved 37 days after the last clinical activity. The paper CRF took 2 work days to elaborate and the transcription process took a total of 27 days. Table 7 summarizes the times recorded and lists the performance indicators measured.

Table 7: Summary of time indicators of both systems (time estimative in days)

Task	Paper process	EDC
CRF creation	2	163 ± 16.3 (per developer)
Database creation	0.5	
Time from last clinical trial activity to database lock	50	37
Time from beginning of process to database lock	89.5	185 ± 16.3

The average query response time for the EDC process was 2.8 ± 2.6 days, while in the paper trial the value was 49 ± 48 days. On EDC more than 50% of the queries were answered in 1 day or less, and all queries were answered in 7 or less days, while in the paper process it took 39 days for 50% of the queries to be answered and the slowest query took 191 days to be answered.

Quality indicators

Eight users answered the questionnaires. 67% of them were either very experienced or experienced computer users and 72% referred they had no or very little experience in using EDC systems. All had a very frequent or frequent usage of computers.

Users' perceived usefulness and ease of use of the system

Cronbach's Alpha for the two variables was 0.92 (usefulness) and 0.72 (ease of use). The mean rating for the "usefulness" questions results was 37.1 ± 4.3 and the mean rating for the six "ease of use" questions was 36.1 ± 2.9 (both out of a maximum of 42).

User satisfaction of the interface questionnaire

The result of the Cronbach's Alpha for the second questionnaire was 0.96. Four factors were extracted, according to [15]: *terminology*, *learning, screen* and *system capabilities*. Users rated the

system's interface an average of 159.4 ± 16.7 (out of 189), with top scores for the factors "remembering name and use of commands", "quietness" and "reaction: dull/stimulating".

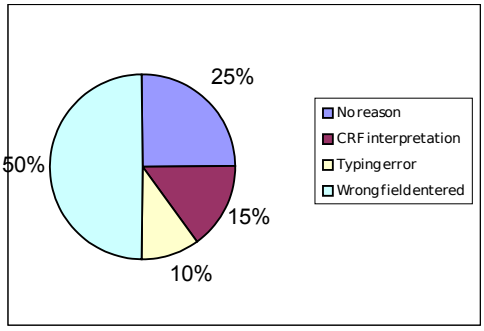

Figure 5: Error type distribution in the transcription phase (total = 20 errors)

Transcription error rate and number of queries

Two users independently double data entered the chosen sample in a database. User 1 made a total of 15 errors, while user 2 made 5 transcript errors. Figure 5 shows the distribution of the 20 transcript errors by type.

After crosschecking the double entry data, two errors persisted in the database. The total error rate in the double data entry process is therefore 1.2 errors per 1000 fields (Table 8).

Table 8: Error rates using different methods, for paper-based and EDC processes

	Error rate (per 1000 fields)
Single data entry	5.91
Double data entry (after crosschecking)	1.2
EDC	0

58 queries were issued after monitorization of the chosen sample, corresponding to a total estimated number of queries of 84. Table 9 lists the queries issued in both processes by category. Criteria violation means that the value in the CRF would imply subject exclusion from the trial. Request for additional information means investigators should have complemented the information entered in the CRF/eCRF (e.g.: a sample collection delay without justification or with "no" answered in the item "were there any relevant incidences?", contrary to what is stipulated in the protocol). Justification of choice made comprises the requests about clinical decisions, such as having considered a lab value "normal" or "abnormal.

Table 9: List of queries issued in the paper and EDC processes, divided by category

Query reason	# paper queries	Estimated total	EDC total
Data consistence	7	10	-
Signature missing	36	52	-
Criteria violation	1	1	-
Other missing data	1	1	-
Other	1	1	-
Request for additional information	12	17	14
Justification of choice made	-	-	13
Data confirmation	-	-	8
Total	58	84	35

Validation summary

Table 10 summarizes the results of the test activities conducted in the pharmacovigilance database. All but 2 of the nine test activities were completely sucessful. Test cases 3 and 4 were partially successful. Reasons for the problems in these tests were a combination of deficient queries for some of the functions and lack of user training to prevent entries from having null values.

Table 10: Validation summary

Test Case	Validation result
Test Case 1 – Function: Save	Success*
Test Case 2 – Function: Edit	Success*
Test Case 3 – Function: Query	Partial success*
Test Case 4 – Function: Report	Partial success*
Test Case 5 - Stress testing of Function: Save	Success
Test Case 6 – Backup procedure	Success
Test Case 7 – Access control	Success
Test Case 8 – Weighted missing values' frequency	Success
Test Case 9 – Weighted error frequency	Success

* - Guidelines are suggested for user interaction with the system

Conclusions

A tailored EDC system was successfully developed and a prototype was implemented and used in a pilot Phase I pharmacokinetic study of a Portuguese pharmaceutical company conducted in Barcelona. A three-tier layer architecture with a thin web client was considered to be the most adequate solution for this system. The data and logic layers were deployed in the same server, therefore hosting the web application and database management system and making performance independent of the client. Centralized process logic also improves maintainability, reusability in different clinical trials and eases scalability, while making the system available anywhere with an Internet connection.

Performance benchmarks showed that the EDC viability is highly dependable on the optimization of its setup time. There was a 17.5 fold decrease in the average query response time and post-clinical trial activities were finished 38% faster in the EDC, similarly to what is written in the literature.

The system's development time is EDC's most time consuming activity. A tailor made EDC system build from scratch is not recommended as a solution for small relatively standardized clinical trials (in number of subjects, time and number of sites). EDC projects should be designed so that database and interface modifications are minimal on subsequent clinical trial projects, decreasing overall setup time.

Data quality was improved when using this EDC system. Transcription errors are present even when using the paper-based's gold standard, double data entry. The number of queries dropped 58.4% when using EDC. This fact is amplified with the decrease in the average response time to suggest both a quality and performance advantage of EDC over paper.

Several factors throughout the project indicate that change from paper to EDC cannot be successfully achieved without the involvement of all actors in clinical trial research. This switch is not exclusively an IT task, but a whole process change, requiring willingness from the people involved and several iterations to be optimized.

A general validation process for electronic data capture systems was developed. The framework of

steps was applied to the validation of a pharmacovigilance system that stores Suspected Adverse Events' (SARs) information in electronic format. The SARs are associated with drugs tested in clinical trials or already launched to the market.

The validation process should start as soon as possible in the software's life cycle, and activities are performed according to a Validation Plan. All stakeholders should participate in the elaboration of the Validation Plan. The clear definition of the system's requirements and the system's risk assessment are fundamental to define what validation activities must be preformed and the extent to which they are preformed.

The pharmacovigilance system's requirements were created. They included the possibility to insert and modify SARs, view already inserted SARs and create exportable reports. Mitigation strategies were limited to the maintenance of regular backups and security requirements included the limitation of users' read and write privileges.

A Test Plan was developed consisting of nine tests that ensured all the system's functions were working according to their specifications. A traceability matrix made the correspondence between the tests and the system's requirements.

The system was considered to be validated for its intended use, as long as a user guide was developed and users were trained to use it. A periodic review of the system should be made every two years and all documentation regarding the system and its validation should be archived in secure conditions and be readily available to users or regulating authorities.

The validation task proved the importance of the concept of validation in the development of electronic data capture systems in highly regulated environments. The successful validation of a pharmacovigilance system opened the door for the interoperability of different systems in a wider CTMS, which raises the interest of the EDC systems. The eCRF can be developed in the future to interact with a pharmacovigilance system in the automation of SARs' management. In these situations, the full potential of an EDC system can be explored: data mining is easier and inter-trial comparisons (for research or procedure optimization) are possible.

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