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In collaboration with

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

Resumo

O objectivo do projecto consistiu em desenvolver uma interface para um sistema de captura electrónica de dados (EDC) usado num ensaio clínico de biodisponibilidade, avaliar o processo de EDC e desenvolver um protocolo de validação aplicável a um sistema de farmacovigilância presentemente em uso.

Foi criada uma base de dados que pode hospedar vários ensaios clínicos e implementada uma interface para aceder à base de dados. Foi usada uma arquitectura *three-tier,* tendo sido implementada um cliente fino acessível via web. Foi desenvolvido um plano de validação tendo em conta o risco inerente à base de dados de farmacovigilância e os seus requisitos. Criaram-se nove testes, executados de acordo com um plano de testes para avaliar o estado de validação do sistema.

Os erros de transcrição do processo em papel foram de 1.2/1000 (entrada dupla de dados) e 5.91/1000 (entrada simples). O EDC eliminou este passo e, consequentemente, os erros de transcrição. O número de queries diminuiu 58.4% no processo EDC e foram resolvidos 17.5 vezes mais depressa, enquanto que o tempo desde o início do projecto até ao encerramento da base de dados aumentou de 89.5 dias para 185 ± 16.3 dias. O tempo desde o último procedimento clínico até ao encerramento da base de dados diminuiu 38%.

Houve um aumento geral nos indicadores de performance e de qualidade no protótipo EDC, exceptuando no tempo total do projecto. Os sistemas EDC devem ser desenhados para que as modificações à base de dados e interface sejam mínimas na aplicação a ensaios clínicos subsequentes.

Sete dos nove casos de teste de validação foram bem sucedidos. O sistema de farmacovigilância foi validado, tendo sido feitas sugestões em relação ao treino dos utilizadores do sistema.

Palavras-chave: Captura electrónica de dados, ensaios clínicos, validação, benchmarking

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Abbreviations

AE(s)	Adverse Event(s)
AIF-HSCSP	Area d'Investigació Farmacologica Clinica do Hospital de Santa Creu i San Pau
AR (s)	Adverse Reaction(s)
ASP	Active Server Pages
CRF	Case Report Form
CTMS	Clinical Trial Management System
DBMS	Database Management System
DMED/GT	Medical Department of Grupo Tecnimede
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	European Agency for the Evaluation of Medicinal Products
E-R	Entity-Relationship model
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IIS	Internet Information Services
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
QPPV	Qualified Person for Pharmacovigilance
SAR(s)	Suspected Adverse Reaction(s)
SAS	Statistical Analysis System
SPS	Summary of product's characteristics
SPSS	Statistical Package For Social Sciences
SQL	Structured Query Language
UML	Unified Modeling Language
US	United States

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1 Background

1.1 Clinical trials

1.1.1 Clinical trial data

The various periods of a single clinical trial are defined as screening, baseline, treatment and post-treatment [1].

The screening period's purpose is to evaluate the eligibility of subjects to enter the trial. It is common to conduct in this period a series of clinical tests such as a physical examination, an ECG or laboratory exams. The baseline and treatment periods are aimed at collecting the variables of the study and the post-treatment period's objective is to check for withdrawal effects and ensure patient safety. The post-treatment evaluation and data collection may be conducted by telephone or with a physical medical interview.

The ICH, which brings together the regulatory authorities of Europe, Japan and the United States, has issued several guidelines on clinical trials, from planning to execution. The Efficacy guidelines (E1 to E15) refer both efficacy and safety data that should be collected throughout the clinical trials.

ICH's guideline E9 - Statistical Principles for Clinical Trials defines the primary variable of a clinical trial as the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial [2]. The primary variable is usually an efficacy variable although safety and tolerability may also be the primary variable. Secondary variables can also be used either as supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. All variables must be clearly defined in the clinical trial's protocol.

1.2 Data management in clinical trials

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 [3]. Data collected in clinical trials is the determinant factor to determine drug safety and efficacy. During clinical development data must be collected and analyzed 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 [4]. 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 r*ecord all of the protocol required information to be reported to the sponsor on each trial subject [5]. 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 (e.g., hospital records, clinical and office charts, laboratory notes, subjects' diaries or evaluation checklists, pharmacy

dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, magnetic media, x-rays, subject files, and records kept at the pharmacy) [5].

The typical process of data capturing in clinical trials is paper-based. According to CenterWatch the percentage of trials conducted using paper was 85-90% [6] in 2003. The remaining trials used an electronic data capture (EDC) process. The traditional process of data flow is illustrated in Figure 1 (adapted from [7]).

After all the study material required is delivered (1), participants (healthy volunteers or patients) are enrolled in the clinical trial (2). This enrollment is made before checking if participants satisfy the inclusion criteria and do not possess any of the exclusion criteria defined for the trial. After the CRF is completed (3), the first task of the investigator and the sponsor's monitor is to verify data in the CRF against the source data (4). The goal of this task is to compare data between the CRF and source data to ensure the validation of the CRF. Afterwards, a clinical data storage system (such as an electronic database) is built and data is entered in this system (5). Data can be entered by one or more operators, being named single data entry if only one person is entering data and double entry if data is entered on two independent occasions (either by two operators or by one operator on two separate occasions). Being a manual process, it is possible that transcription errors can occur.

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 [8]. 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 [9]. 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% [10].

After data in the database is validated (6) by cross-checking the two independent databases (if a double data entry process was adopted), forms are sent to the investigator every time the sponsor finds data they believe is incorrect, such as a therapy date being before the consent date. This form has several names but is often called a Data Clarification Form (DCF) or, more simply, a query (7). The investigator will respond to the query entering the correction or the explanation for the data on the DCF (8) and the database is updated (9). This process is interactive and will occur until every question is answered. By then, the database is closed and data can start to be analyzed (10).

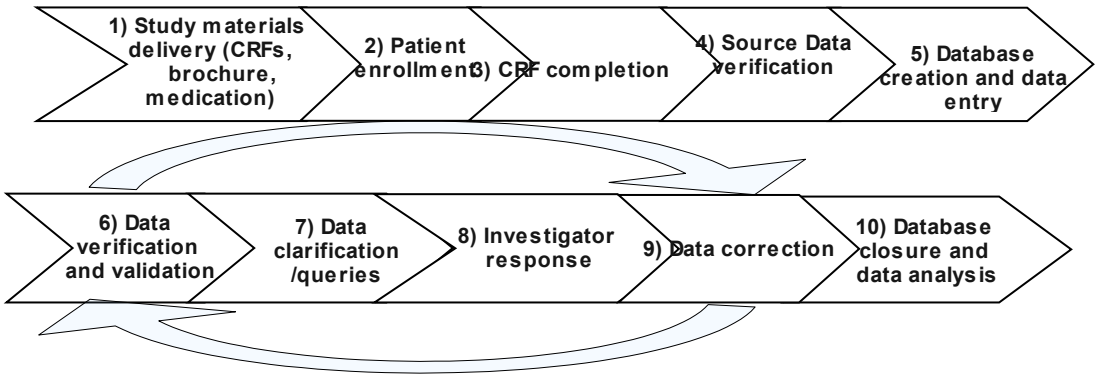


Figure 1: Typical data flow in a clinical trial

An alternative to the paper-based process in clinical trial data capture is an EDC process. The main difference is the collecting media used to capture data. Instead of using a paper CRF, an electronic case report form (eCRF) is used and data is introduced directly into an electronic system.

Figure 2 compares data flow using the two processes and it graphically illustrates the differences in terms of types of action taken in the intermediate steps. Both processes start with data being collected from the source documents (far left side) and end with information in a database and ready to be analyzed (the blue file cabinets on the far right side). The main difference between the two processes is the time frame in which events occur. In the paper-based process there is a time lag between the time data is collected and the moment the information is available for the data manager: CRFs must be sent to the sponsor's site, compiled and data entered by two operators and cross-checked (time frame between steps 3 and 6 in Figure 1). Because data is entered directly in the database using EDC, these steps are eliminated. No physical CRF must be transported back and forth between the research center and the sponsor and data entry in step 5 (Double data entry section in Figure 2), so there is a considerable time save that can reduce the total cost of data management in clinical trials. Automatic edit checks of an EDC system can also reduce the error rate in data entry. An edit check is a control system to guarantee data is introduced in a logical way (e.g. therapy date must be after the consent date, height or weight must be non negative numbers) and, contrary to a paper CRF, it can be implemented in an EDC system.

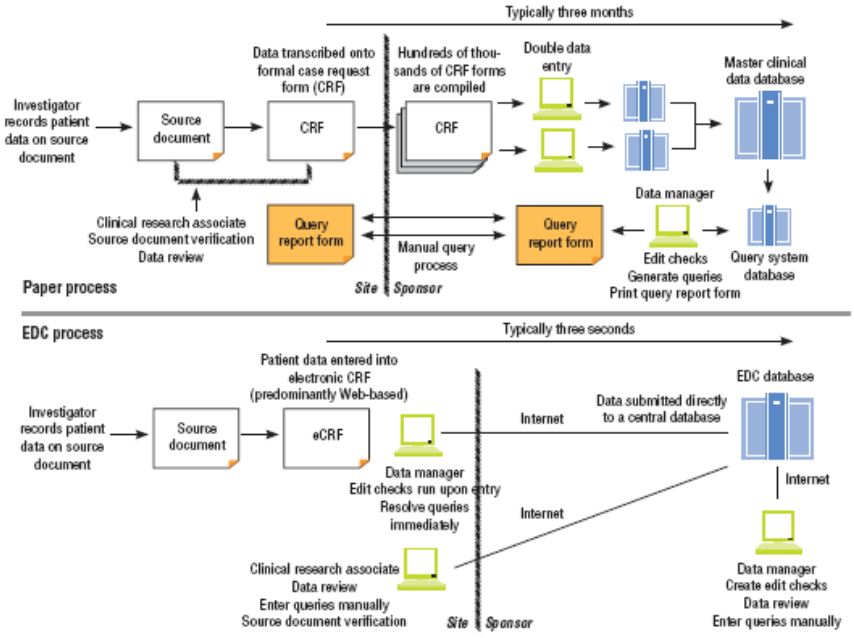


Figure 2: Paper-based vs. EDC data flow in a clinical trial [11]

Another advantage of using an EDC solution is query management. Because data is available to the data manager immediately after it has been introduced, the data verification and validation process (6) can start earlier. Queries can be sent by the monitor to the investigator sooner than in the paper-based case (where typically months can pass between data entry by the investigator and query issuing) which will contribute to data quality. Table 1 summarizes the main advantages and disadvantages of an EDC system.

Table 1: EDC advantages and disadvantages over the traditional paper-based process of data collection in clinical trials (adapted from [12])

EDC characteristic	Advantage/disadvantage over paper-based process
Elimination of double data entry	Time and cost savings
Automatic edit checks to eliminate errors	Reduction of queries
Creation of electronic documents (eCRFs)	Elimination of printing, binding and shipping costs, reduction of space at trial sites
e-Monitoring	Time saving, elimination of travel costs
eCRF creation more complex than double data entry	Higher cost per worker
New process for the industry	Resilience from industry and authorities against process change
Hardware and telecommunications dependence	Lack of support in some sites

1.2.1 Efficacy comparison between EDC and paper-based data capture

In 1998 N. Banik presented an efficiency study of EDC versus paper data collection [12]. In this five country, 19-site trial (N= 226 subjects) study, EDC proved to be more efficient than paper, with reductions in clinical trial duration (30%), time to locked database (43%) and number of queries (86%).

Another publication [13] demonstrates an improved efficiency when using EDC after collecting data from ten Phase III studies (N = 6700 subjects in total). The results are depicted in Table 2. Queries caused by missing data and queries requesting clarifications simply are not present in the EDC system. The usage of automatic edit checks and the fact that handwriting does not exist explain the absence of these queries. In other words, the usage of an EDC system can eliminate 54% of all queries.

Table 2: Benefits of EDC usage in clinical trials – side-by-side comparison with paper

	EDC	Paper
Percentage of enrolled subjects that are invalid	7.5%	15%
Cost of raising and resolving a query	$10	$60
Number of queries/subject	0.25 - 1	5 – 20
Percentage of data requiring correction	0.05 – 0.1%	1 – 2%
Percentage of queries caused by missing data	0%	48%
Percentage of queries caused by inconsistent data	5%	35%
Percentage of queries caused by out-of-range data	0.1%	8%
Percentage of queries requesting clarification	0%	6%
Percentage of queries due to invalid data	0.05%	0.1%

Note: Query percentages are based upon number of queries raised when using paper

In 2001, Datatrak published a large study evaluating EDC versus paper to quantify clinical trial costs between the two processes, having concluded that EDC costs were inferior to the estimated paper costs in 18 out of 19 trials studied [14]. The lack of statistical significance between regular EDC budget and a paper-based process in the Phase I trials observed in the study is in agreement with an earlier study that does not recommend remote study monitoring for typically small trials (i.e. small number of sites, few visits) [12].

1.3 Regulation in the US and Europe

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 [15].

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 [16]. Because records generated during drug development must be kept and reported to the regulatory authorities, any EDC system used in clinical trials is therefore under the scope of Part 11 if the study is to be reported to the FDA. Electronic signatures that are intended to be the equivalent to handwritten signatures, initials, and other general signings required by predicate rules [16] are also subject to Part 11 regulation.

An electronic signature is defined as a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be legally binding equivalent of the individual's handwritten signature [15]. A biometric signature is a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or individual are measurable [15] and it is sufficient to be validated as an electronic signature by Part 11 rules. If electronic signatures are not biometric, Part 11 requires them to employ at least two distinct identification components such as an identification code (username) and password.

Electronic records are also subject to control in Part 11, where focus is given to their authenticity, integrity and, when appropriate, confidentiality. Records must be protected and their access limited to authorized individuals in one hand and readily available for inspection, review and copying by the FDA.

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 [15]. An audit trail is therefore a record that allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record and is required to exist in systems under the scope of Part 11.

ICH's Good Clinical Practice guideline specifies under sub-section 8.3.15 that the goal should be to document all changes/additions or corrections made to CRF after initial data were recorded [5]. With an eCRF that complies with the rules defined by Part 11 the level of accuracy in data recording is raised as, in an easier way than in the paper-based model, initial data entries can be individually associated with a date and a user and can therefore also be tracked and audited as subsequent data entries.

Part 11 also requires a collection of additional controls to electronic records' systems to limit system usage by unauthorized users, usage of system checks to determine the validity of data inputs and determination that people that develop and maintain the system have adequate education, training and experience to perform their tasks. Written polities must be present to hold users accountable for actions initiated under their electronic signatures.

In 1999, the FDA issued guidance for the industry on *Computerized systems used in clinical trials* where it summarizes the main requirements of the FDA to ensure quality of electronic data in clinical trials. Table 3 lists the main guidelines that a system should follow if it is to be used in a clinical trial.

In this guidance, the bureau also 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 [17]. Documentation should provide an overall description of the system and the relationship of hardware, software and physical environment.

Table 3: Main characteristics of computerized systems used in clinical trials (source: [17])

Standard Operating Procedures	**SOP -** Should be established for all activities, from system setup to data collection and handling, system maintenance, data backup, recovery and contingency plans, security and change control.
Data entry	**Electronic signatures -** Every data entry must be associated to an electronic signature. The name of the individual who is entering data must be visible. Passwords must be changed periodically and users must log off after leaving the workstation. **Audit trail -** Audit trails must be present and maintained for as long as required for the subject electronic records. The system's date and time must be correct and changes to date or time must be documented.
System features	**Edit checks -** Prompt, flags or other helpful features within the computerized system should be used to encourage use of clinical terminology and to alert the user to data that are out of acceptable range. eCRFs should be designed to allow users to make annotations that add data quality. Systems used for direct entry of data should include features to facilitate data inspection and review of data. Data tags should be used to indicate which data have been changed or deleted. Data should be easily migrated to newer systems.
Security	Physical security should be built to ensure that access to the system and to data is restricted to authorized personnel. Logical security through log-ins and audit trail must be ensured to restrict data access. The names and titles of authorized personnel must be available at anytime, as well as their access privileges.
System dependability	Documentation should demonstrate software validation: written design specification describing what the software is intended to and how it is intended to do it, written test plan based on design specification and test results and evaluation. Written procedures should be available to ensure changes on the system, such as software upgrades or hardware changes.

System controls	Contingency plans should be in place for the event of failure of the system. Backup and recovery procedures should be clearly outlined in the SOPs and be sufficient to protect against data loss.
Training of personnel	**Qualifications –** each person who enters or processes data should have education, training and experience necessary to perform the assigned functions. **Training –** training should be performed to provide individuals and conducted by qualified individuals. **Documentation –** employee education, training and experience should be documented.
Records Inspection	Systems should be able to generate accurate and complete copies of records in both human readable and electronic form for the FDA.
Certification of electronic signatures	Electronic signatures must follow CFR Part 11 rules – certification that the electronic signature is legally equivalent to handwritten signature must be sent to the FDA prior to system usage.

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.

The FDA guidance specifically notes the case of database software, where design level validation may not be possible to achieve. In this case, the FDA suggests that the sponsor performs functional testing (using test data sets) and researches for limitation, problems and defect corrections in the software.

Table 4 lists the documentation the FDA suggests to be available by the sponsor to demonstrate the validation of the software used in clinical trials.

Table 4: Documentation to demonstrate software validation

Documentation to demonstrate software validation
Written design specification describing what the software is intended to do and how it is intended to do it
Written test plan including both structural and functional analysis
Test results and evaluation of how these results demonstrate that the design specification has been met

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” [18]*. Given this definition, it is commented by the FDA that an established software requirements specification is essential for the software validation process to take place.

The FDA guideline also describes the typical tasks supporting software validation. Table 5 lists these tasks and briefly summarizes the FDA view on which activities should be conducted on each task group.

Table 5: Tasks supporting software validation

Tasks	Description
Quality planning	Identification of the necessary tasks, resources, procedures for abnormality reporting and resolution. Identification of the software life cycle model and associated activities.
Requirements	Identification, analysis of information about the device and its intended use, including a written definition of the software functions. Safety management, including identification of potential software failures and mitigation procedures.
Design	Translation of the requirements into a logical and physical representation of the software. Design should include generation of test plans for software modules, their integration, as well as system and acceptance.
Construction or coding	Code or assemble together previously coded software components to build the new application.
Testing by the software developer	Run the software product under known conditions with defined inputs and documented outcomes, which can be compared to their predefined expectations.
User site training	Document inspection and testing to demonstrate proper installation. Evaluation of the ability of the users of the system to understand and correctly interface with it.
Maintenance and software changes	Definition of the tasks and activities that should be performed in the event of changes to the software, either corrective or perfective maintenance.

In the case of off-the-shelf software, the FDA recommends auditing the vendor's design and methodologies used when building the system. In the case of vendors not having a documented life cycle process – or when the vendor does not permit an audit - “black box testing” (i.e. testing of the outputs produced with predetermined inputs and comparison of these outputs with predefined output expectations) should be performed to establish that the software meets its intended use.

In Europe, the EMEA has not issued specific guidelines or regulation regarding electronic data capture in clinical trials. As a part of the ICH, European regulatory authorities follow the ICH guidelines and transpose them to national legislations. Although there is no official position, the rule of thumb in the industry is that, in case of regulation void, each regulatory authority trusts on the rules imposed by reference regulatory authorities. Therefore, an EDC system that is in compliance with the FDA standards should be approved by European Union national agencies.

Although there are no guidelines or rules on the use of EDC systems or electronic records in Europe, the EMEA created the EudraCT, a database of all clinical trials commencing in the Community from 1st May 2004 onwards, which is one step further towards electronic data integration.

In Portugal, clinical trials for human medicines are regulated by the Portuguese Law n.º 46/2004, of August 19th and compliance to the law is supervised by INFARMED. As with the EMEA, there is no reference to Electronic Data Capture or Electronic Data Capture systems.

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities which aim for the harmonization of what are understood to be Good Manufacturing Practices (GMP) in the pharmaceutical industry. The Good Practices are important as they serve as guideline for inspectors of the different regulating authorities.

In September 2007, the PIC/S published a revision of its *"Good practices for computerized systems in regulated GxP environments"* guidance [19]. 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 .*

As in other guidelines the PIC/S guideline suggests that the level of validation required for a particular software depends on the risk associated with its usage. The assessment of the risk associated with the software should therefore be part of the software development process. In addition to this, the validation process definition should also take into consideration the business model of the software subject to validation and the current stage of the software in the life-cycle. For software bought from an external vendor, cooperation with the vendor is essential to satisfactorily assess the validation state of the product, while software already in use (and for which prospective validation might not be possible) retrospective validation should be performed.

In concordance with the FDA guidelines, the PIC/S guideline also stresses that there is no preference for one software development model over another, but that it is important that the validation strategy is adopted as early in the software life-cycle as possible.

2 State of the art

The vast majority of EDC systems available are developed by private companies. Figure 3 shows the US market share in 2004 in terms of Clinical Trial Management Systems (CTMS), where it can be seen that Oracle Clinical and Phase Forward are the two major companies in the CTMS market.

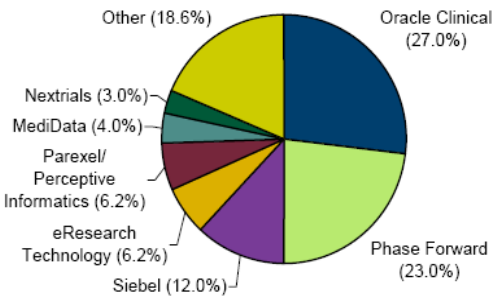


Figure 3: Software License revenue share by Clinical Trial Management Systems Vendor in the United States, 2004 (figure represents 60% of total market share, total market share estimated to be $130 million in 2003) [20]

A Clinical Trial Management System is a set of components that are used in different phases of the clinical trial but ultimately have the same goal [21].

The EDC application is the part of the CTMS responsible for capturing data, allowing query functionality, import data from ePRO - electronic Patient Reported Outcomes (electronic Patient diaries) – lab or ECG exams, and export data to the CTMS system.

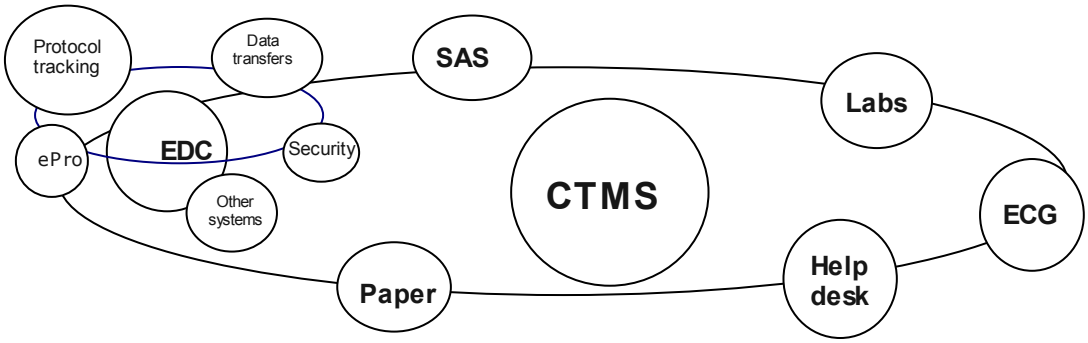


Figure 4: The CTMS world and the role of EDC (adapted from [21])

Although EDC systems can exist without a CTMS , both Phase Forward and Oracle Clinical have EDC integrated in a broader CTMS solution. Most companies provide products offering a subset of the complete CTMS solution [20].

Figure 5: Typical CTMS solution (adapted from: Medidata)

Figure 5 shows a typical CTMS solution consisting of 4 modules for EDC in clinical trials: an EDC interface (capture); a module for building that interface (architect); a component that integrates and manages data collected in clinical trials (manager); and a component that enables automatic reporting, exporting it to various formats (reporter). Most EDC corporate vendors tend to offer these modules. The key aspect of gathering different modules is data integration.

2.1 System architecture

Current EDC systems are mainly web-based and constructed in a three tier architecture. In this type of architecture, the client machine acts as a front end and does not contain any database calls. The client end communicates with the application through an application interface which, in turn, communicates with the database system to access data. In these systems, the business logic is embedded in the application server and not in each of the clients. This is particularly relevant when considering large, multinational phase III trials, where the number of centers (and therefore workstations) is large.

An Internet connection is required in this model. Although smaller devices such as Personal Digital Assistants (PDAs) can be used, the typical application is developed for common web browsers with PC screen resolutions. The client side interface is usually built in the form of a web portal and it uses a secure connection (such as an SSL connection) to communicate with the remote server.

3 Motivation

As described, although EDC is gaining importance as a valid alternative to the paper-based method for data collection in clinical trials, this advance is more visible in North America and it is almost exclusively done in private companies.

In Portugal there are neither known companies dedicated to EDC, nor EDC projects conceived and implemented by private or public institutions. The Portuguese pharmaceutical R&D is dominated by the presence of some hospital based investigational centers that focus their clinical trial activities in the recruitment of subjects for phase III multicenter trials sponsored by big pharma companies.

Grupo Tecnimede is an international pharmaceutical group based in Portugal with resources allocated to chemical, pharmaceutical and early and late clinical R&D programs. The DMED/GT developed a clinical trial protocol for a pilot bioavailability study an oral agent used in the treatment of obesity. The study is characterized as being a Phase I, pharmacokinetics, bioavailability, two-way, cross-over, randomized, open-label study, in six healthy subjects under fasting conditions. As with previous trials, data is captured using a paper-based CRF and later transcribed to an electronic database using the double data entry process.

An alternative to the paper-based process may enable faster data collection and more efficient data management. Such system would imply an important process change in the company and requires planning. An EDC system for clinical trials is part of the larger CTMS project and it can be tested as a first pilot in the development of such a system.

This study gathers a set of characteristics that make it an interesting candidate for the pilot. Table 6 summarizes the characteristics that can become an advantage as a pilot study for a broad EDC solution for the company.

Table 6: Study characteristics

Study characteristic	Advantage for EDC pilot
Small number of subjects	Controlled study
One study center	Small number of staff to train
Adequate time schedule	Three week study, controlled time frame
Study center in Barcelona - AIF-HSCSP	e-Monitoring’s advantages are easily understood

The development of such a system must be in compliance with the rules and guidance defined by regulatory authorities. The publication of the PIC/S' Good Practices for computerized systems guideline revision was a significant step in the harmonization of the areas of focus that should be considered in inspectorate activities. The creation of these guidelines gave clear indications on how to proceed to determine the adequacy of software systems to their intended use and it gave tools to audit the validation activities associated with the software. Consequently, it is expected that European regulatory authorities in general – and Infarmed in particular – dedicate increasing attention to the validation state of all software used in the industry's activities.

Everytime a suspected adverse reaction (SAR) occurs in a clinical trial, it has to be recorded on the CRF. If the reaction is classified as serious, it has to be reported to the regulatory authority within 15 days. Infarmed also requires that information about SAR on all drugs in the market must be recorded and stored on a specific database for archive. This means that a system should exist to record and archive both AE that occur during clinical trials and spontaneously in all products in the market. This repository of the information is commonly referred to as a pharmacovigilance database and information is received through (1) a notification made by Infarmed, (2) a notification sent by doctors, pharmacists or other healthcare professionals (HCP) or (3) a notification made directly by the patients (consumers).

Tecnimede developed a pharmacovigilance electronic database in the early 2000's. This system is home-made and it was updated in 2006. The electronic system consists of a database developed in Microsoft Access. To accomplish the recent guidelines on software validation, Tecnimede wants to validate its pharmacovigilance system. There are currently no known companies in Portugal that provide the service of validating an existing software.

The success of the project is directly associated with the capability to understand the particularities of the pharmaceutical development process and the ability to development a tool that makes work easier for all the stakeholders. The Biomedical Engineer is a key member of building a bridge between tclinical R&D and Information Technologies. The Biomedical Engineer has the ability to understand the problem from the Health Sciences' point of view and on the other hand, has technical IT training that enables him/her to plan and execute the tasks required to solve the problem.

Validating the pharmacovigilance system enables the identification of the main areas of focus when preparing a software for compliance with the industry. It also opens the possibility to the integration of the pharmacovigilance system into the eCRF system developed for the clinical trial.

4 Objectives

The goal of the global project is to develop a tailored EDC system to be used in a bioavailability clinical trial and use performance and quality metrics to benchmark this process against the traditional paper-based method. Complementarily, a pharmacovigilance database was validated

The project includes planning and creating a database structure for clinical trial projects and an interface to access the database. While details about the database will be discussed elsewhere [25], the primary objective of this work was the interface development, evaluation of the EDC system and the creation and execution of a validation protocol for the currently active pharmacovigilance system.

This work is pioneer in Portugal. EDC systems are developed either in-house or in outsourcing. Details about the development of such a system from scratch are unavailable. Validation of software has only recently been subject to interest by inspectorate and this service is not provided by the main IT services companies in Portugal. This work will not only shed some light into the subject but also use performance metrics to determine the long term potential gains of using EDC as the default process to retrieve and review data in bioavailability Phase I clinical trials.

5 Methods

The development of the EDC system comprises the following phases:

- *Requirements elicitation*

The development team had to define the main characteristics of the system in terms of its business and functional requirements. The description had to cover the basic inputs and outputs of the system to allow future data integration in a CTMS project.

- *System analysis and design*

Taking the description of the business requirements, a high level design of the system had to be created. The key to this step was to develop a picture of the distinct objects that make up the system. In particular, the operating system under which the system would run had to be defined, as well as the development tools – programming tools and database management system (DBMS) – used to build the EDC system.

- *Object design and implementation*

This phase consisted of designing the specific system components, including the UML (Universal Modeling Language) diagrams for the interface and the E-R diagram of the database. Although reference to the complete project was made and the main concepts of the whole project were explained, emphasis was given to the interface design and development. Details on the data and database aspects are explained elsewhere [25]. A functional prototype was developed and tested in the EudraCT 2006-002028-40 clinical trial.

- *System benchmarking*

The EDC process was evaluated in terms of performance and quality. Table 7 lists the indicators that were chosen to evaluate the system. These metrics are amongst the most commonly used in the industry [22]. Performance indicators are measures of the data management time required to prepare, execute and conclude the clinical trial. Although the term *quality* is not related with any tangible measure, some measures of a system may be identified with the process' *gold standard*. Quality indicators are therefore objective measures that can be related with the ideal system. In a clinical trial, the absence of transcription errors in data collection and the absence of queries are properties of an ideal system. Satisfaction of users with the CRF used can also be a measure of quality. Perceived usefulness and ease of use and user satisfaction indicators were determined by questionnaires send out to users.

Table 7: Performance and quality indicators used to evaluate the EDC system

Metrics	Indicator type
Time between the beginning and end of the project	Performance
Time between last clinical procedure and database lock	Performance
Average query answer time	Performance
Number of queries	Quality
Transcription error rate	Quality

Perceived usefulness and ease of use	Quality
User satisfaction	Quality

The validation of a computerized system is, in the context of pharmaceutical industry's activities, a process to create a sufficient level of confidence for the company and regulatory authorities that the system meets all requirements and user expectations for its functions and features.

The validation of the electronic system encompassed the following steps:

- *Determination of the life-cycle phase the software is currently in*

Validation should start as early in the life-cycle phase as possible. The first task was to determine the current state of the software being validated. In the event of a legacy system or a system developed by a third party, all documentation regarding the system and its production should be gathered so it can be subject to inspection. A crucial document that must be collected is the definition of the system's business and/or functional requirements.

- *Determination of the level of validation that is necessary for the system*

As mentioned previously, what is understood as a “sufficient level of confidence that the system meets requirements and expectations” depends on the risk associated with the software. A software whose malfunction can have consequences that may endanger the patients' health or life, for example, should be subject to a more thorough validation process than a system that has no influence over these factors.

When developing a protocol for validating an electronic system, some sort of a risk analysis should be created that helps defining the boundaries of the validation activities.

- *Definition and execution of a validation plan*

The validation plan is the document that describes which validation activities will be performed and how they will be carried out. It also describes what the expected behavior of the system should be when it is subjected to pre-determined input conditions.

Taken into consideration the findings of the previous steps, a validation plan for the pharmacovigilance database was defined. This activity included the creation of a test plan with all the tasks that were executed.

- *Elaboration of a validation report*

After executing all the tasks defined in the validation plan, a validation report was elaborated. The validation report summarizes the findings of the validation activities and illustrates the validation team's final view on whether the system should or should not be accepted for use.

5.1 Requirements elicitation

Every project begins with determination of the necessities. This project began with the idea for an electronic method for capturing data in a Phase I clinical trial.

Naturally, this view from the DMED/GT was somewhat vague in terms of software development. Nevertheless, this initial process is an especially critical part of the process. In 1994, the Standish Group surveyed over 350 companies about their over 8000 software projects [23]. Thirty one percent of the projects were canceled. Among the top factors for software development failure are incomplete requirements (13.1%), lack of user involvement (12.4%), lack of resources (10.6%) and changing requirements and specifications (8.7%). Requirements elicitation and definition are involved in almost all of these causes.

Table 8 lists the main requirements of the system as viewed by the pharmaceutical company.

Table 8: Grupo Tecnimede's system requirements

Requirement	Description
Compliance with Part 11 and FDA	Compliance with the FDA's standards is a step in the direction of European approval
Similarity with paper CRF	To avoid process change resilience by system users, eCRF should emulate the CRF whenever possible
Definition of user roles	Users should have different roles – project manager, investigator and monitor – and specific task permissions
Data exportation	Data must be exportable to standard formats

In short, the eCRF had to be as similar as possible to the paper CRF that was used simultaneously in the study to prevent the introduction of external variables when comparing the two systems.The system had to comply with FDA's requirements, namely with CFR 21 Part 11.

Four different types of users would use the system: (1) the investigator is the user from the research center that actually enters subject's information in the CRF; (2) the monitor is the person from or acting on behalf of the pharmaceutical company that reviews the CRFs (and eCRFs in the EDC case) to check for data validity; (3) the project manager is the sponsor's primary responsible for the project and supervises all the activities. It is the project manager's responsibility to close and lock the database, i.e. prevent further changes to a clinical trial's database; (4) finally, a system administrator must also exist to supervise technical aspects and ensure system stability and performance.

Data must also be exportable to standard formats, such as PDF or Excel, to allow later data manipulation.

After defining the business requirements, they had to be translated into functional requirements of the system.

To comply with Part 11 requirements the system's electronic signature may be implemented with a username login and a password. Information shall 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 shall log off when leaving their workstations. These requirements

should eliminate the possibility of a user accidentally using the system while under a session that is not his own.

Section 11.10 (e) of Part 11 forces electronic systems to use a secure, computer-generated, time-stamped audit trail to independently record the date and time of operator entries and actions that create, modify or delete electronic records. The record changes shall not obscure previously recorded information and shall be retained for a period at least as long as that required for the subject electronic records. In other words, an audit trail is a functional requirement of the system and no information can be deleted from it.

Also regarding data safety, the system shall 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 shall be recorded and special clearance will be 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 shall 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 must be able to quickly access information. A query system must be in place so that the monitor can perform his tasks .

Data interoperability shall also exist both in input and output perspectives. Laboratory results regarding plasmatic concentrations of the primary variables are sent by the laboratory in Excel format and an automatic import system is 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 9 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) [23].

Table 9: 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

5.2 System analysis and design

5.2.1 System architecture

Taking the functional requirements into account, a high level design of the system must be made to define its main architecture. The requirements are mainly related to two distinct aspects: *data* and *data manipulation and access*. This clearly suggests a multi-tier architecture where data and interface are separated. The concept was already introduced when reviewing system architectures in the State of the art section. Figure 6 recalls the three-tier architecture, which will be used in the EDC system.

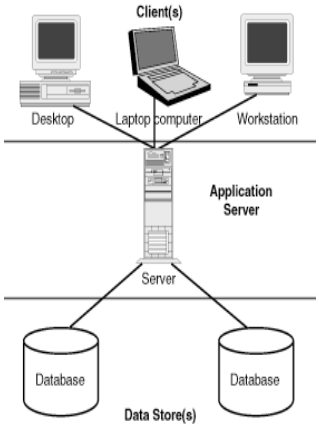


Figure 6: Three-tier architecture proposed

The three-tier architecture is composed of three distinct layers:

- The data layer (the lowest layer in Figure 6) provides database management functionality and is dedicated to data management. This component ensures that the data is consistent throughout the distributed environment through the use of features such as data locking, consistency and replication. These features are available in most available Database Management Systems (DBMS) (see [25]).
- The application layer (middle tier in Figure 6) is responsible for most of the business logic of the system. It is built on the server end of the system and it therefore improves performance, flexibility, maintainability, reusability, and scalability by centralizing process logic. Centralized process logic makes administration and change management easier by localizing system functionality so that changes must only be written once and placed on the middle tier server to

be available throughout the systems. This middle tier also manages distributed database integrity by the two phase commit process.

- The presentation layer (upper tier in Figure 6) is a thin client that serves as the interface for the user. In this EDC implementation the presentation layer will consist of a web interface that can be accessed using a common web browser. The consequence of this implementation is a very light client that is only responsible for the interface presentation to the user, while all the business logic is processed in the backend.

After choosing the system's architecture, other choices had to be made regarding the technology tools that were to be used. There are several similar choices for the different abstraction layers of the architecture. In terms of DBMS commercial systems like Oracle, MS SQL Server 2005, MySQL and PostgreSQL are the most common options. There are several options regarding web server and client side architectures. The most common are ASP (current version is the .NET technology), Java (jsp, jsf) and PHP. The most common web servers are Apache and IIS, with approximately 61 and 31% of total market share, respectively [24].

Microsoft's ASP.Net framework was chosen to develop the interface prototype and MS SQL Server 2005 was chosen as the DBMS. The previous development experience in SQL Server 2005, the knowledge in the coordinator's group on .NET technology, and the perfect integration between the three conceptual layers due to being part of the same development framework, were the main reasons behind this choice. Because ASP .NET can only natively run under Internet Information Services (IIS), and SQL Server 2005 only runs under a Windows operating system, the server was built in a Windows XP machine.

5.2.2 Clinical trial details

This clinical trial was a cross-over, open-label, randomized, bioavailability study 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 and will from now on be referred to as Period 1 and Period 2. These periods were preceded by a screening period and followed by a final control period.

Each of these four periods was, in turn, composed of several procedures (Table 10).

The Screening phase essentially serves to evaluate subjects' eligibility to enter the clinical trial. Participants' demographic and medical history were collected and a blood analysis was also conducted to check every laboratory item listed in Table 10. Laboratory data results, ECG and every other source documents had to be attached to the CRF. In the paper-based method this was physically achieved with the help of a staple. At the end of the screening process, the inclusion and exclusion criteria were checked. If the subject met the trial's requirements, he was given a volunteer number, and was considered able to participate in the clinical trial after being instructed about the trial's procedures and restrictions.

Table 10 – Study procedures

PROCEDURE	Screening	Period 1	Period 2	Final Control	Upon adverse event*
Informed Consent	X				
Medical history and concomitant medication	X				
Physical Examination	X	X (upon completion)	X (upon completion)		X (if required)
Vital Signs	X	X (upon completion)	X (upon completion)		X (if required)
ECG	X				
Biochemistry Albumin, Alkaline phosphatase, AST, ALT, BUN, Calcium, Chloride, Glucose, Phosphate, Potassium, Serum creatinine, Sodium, Total bilirubin, Total protein	X			X	
Hematology Complete blood differential count, Hemoglobin, Haematocrit	X			X	
HIV and Hepatitis Hepatitis B (HBs Ag), Hepatitis C (HCV), HIV antibody	X				
Urinalysis (macroscopic examination) pH, Specific gravity, Protein, Glucose, Ketones, Bilirubin, Occult blood and cells, Nitrite, Urobilinogen, Leukocytes, Microscopic examination (will be performed on abnormal findings unless otherwise specified)	X			X	
Urine Drug Screen Amphetamines, Barbiturates, Benzodiazepines, Cannabis, Cocaine, Opiates	X				

- Additional exams could be performed whenever the Principal Investigator considers appropriate for safety reasons

Period 1 and 2 are equal in terms of data collection. Subject's condition was checked for clinical or analytical changes and they were questioned about any concomitant drug administration during the periods' interval. If investigators decided the volunteer could be maintained in the study, he was administered the drug that he had previously been randomized to take. During the course of three days, 24 blood samples were collected. The actual times were recorded to ensure no delay existed between sample collection and the theoretical time written in the protocol. One disadvantage of the paper-based model is that the relative time used against drug concentration is the theoretical – protocol determined - relative time. If, by any chance, there are delays in sample collection, the actual relative time will differ from the theoretical value. Figure 7 illustrates what has been said. The EDC system can eliminate this mistake by automatically recalculating this real relative time.

An abbreviated physical examination and the vital signs were collected at the end of each period.

The final control was performed a few days after Period 2. Blood analyses were repeated to ensure subjects' values remained normal and investigators filled out information about study completion (if subjects can complete the study and, if the answer is negative, the reasons for abandoning the study).

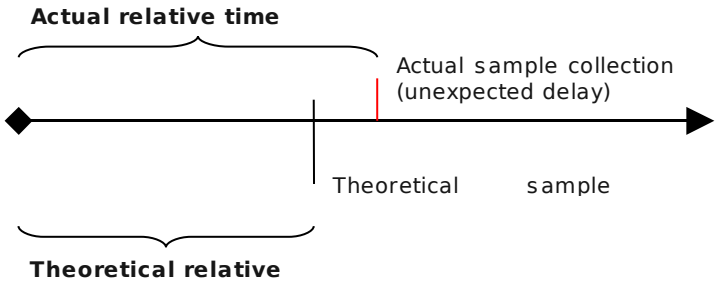


Figure 7: Difference between theoretical relative time and actual relative time

Throughout the CRF pages investigators can write down relevant comments, either on specific spaces created for that purpose or simply on a blank part of the page. One of the FDA's recommendations on eCRF is precisely the ability to make annotations which can add data quality by allowing ad hoc information [17].

In the CRF closeout the principal investigator and the quality assurance unit review data contained on all pages of the CRF and certify their accuracy, completion and trueness by means of a dated signature.There are two additional events that can occur on any day throughout the clinical trial. The subject can have an adverse event and/or need to receive a concomitant treatment.

An adverse event (AE) is described in the trial's protocol as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any AE that is judged to be serious and/or unexpected has to be reported to the regulatory authority.

A serious adverse event is that which a) Results in death; b) Is life threatening (refers to an event in which the patient was at risk of death at the time of the event; c) Requires inpatient hospitalization or prolongation of existing hospitalization; d) Results in persistent or significant disability/incapacity or e) Is a congenital anomaly/birth defect. An unexpected adverse event is an adverse experience, nature or severity of which is not consistent with medicinal information in the relevant source documents (e.g. SPS). A concomitant medication is any drug product that needs to be administered during the trial's period. All concomitant medication must be reported in the CRF.

5.2.3 Use cases

The system's functional requirements refer user authentication and different privileges depending on the user's role. This section is intended to describe all the system's user roles (actors) and the tasks that can be performed in the system (Use Cases), using its interface. It also describes which tasks each actor can perform.

There are six different actors in the EDC system: the anonymous user, the monitor, the investigator, the data manager, the project manager and the system administrator.

Table 11: Actors and their description

Actor	Description
Anonymous user	Any user that accesses the web site where the EDC system is hosted
Monitor	The user responsible for data review and verification and for query issuing
Investigator	User responsible for entering subjects' data in the eCRF and answering queries
Project manager	The sponsor's user who is responsible for clinical trial planning
Data Manager	The user responsible for data verification after the monitor finishes his work
System Administrator	The independent user responsible for administering the system and ensuring its correct behavior

Use cases description

Table 12 lists and describes the system's use cases. Annex A gives a more detail description on each use case, as well as the definition of the previous steps required before each use case is performed.

Table 12: System's use cases and description

Case	Description
Access validation	How users are validated before using the system and the database
Add subjects to trial	How users add a subject to the clinical trial
Automatic Edit Checks (performed by the system)	How the system performs edit checks
Data entry and data changes in the eCRF	Which users can edit the different parts of the eCRF
View eCRF data	What sections of the eCRF each user can see
Subject exclusion	How a user can exclude a subject from the trial
eCRF (un)Lock	How users can lock/unlock a subject's eCRF
Query issuing	Steps monitors must follow to issue a query
Query answer	Steps investigators must follow to reply to a query
Trial data export (including audit trail export)	How clinical trial's data and audit trail can be exported to different formats
Drug concentration data management	Specific instructions on how drug concentration data is managed
Clinical trial data lock	How the clinical trial can be locked
Clinical trial unlock	How the clinical trial can be unlocked for further edition
Insert source documents	How the source documents can be inserted in the database
Create user accounts	How user accounts can be created
Database administration	How can data be directly edited using SQL commands

Naturally, not all tasks are available to every actor in the system. The permissions given to each actor in the system are summarized in Table 13.

Table 13: 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

5.3 Object design and implementation

5.3.1 Website navigation

The website design started with defining the different objects that make up the interface and how these objects are connected. This could be achieved through a website navigation map that showed what pages were present in the interface and how users could browse through them to perform their tasks. The interface design for the system is represented in Annex B.

In a short description of the design, the interface was composed of four vertical layers that are connected: 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 8 exemplifies the four layers that a user would navigate through while performing a task in the case of an investigator using the system to enter some data. After a user had successfully authenticated in the system, he would select the clinical trial he was interested in; he would be sent 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, he would be 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), he would be sent to the specific task's layer, where he could enter data. When the user was finished using the system he would log out and was sent back to the login layer.

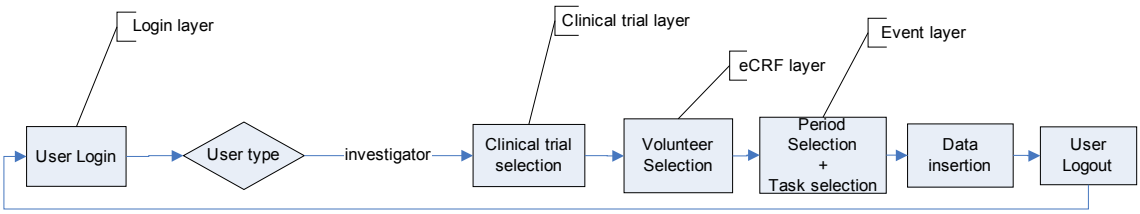


Figure 8: Navigating through the different interface layers

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. This concept is further explored elsewhere [25].

Because a detailed analysis of each component of the interface would be cumbersome, a general overview of the different layers will be presented.

Login layer

This is the interface layer to access the system. The only available action is log-in to the system, which will lead the user to the clinical trial layer.

Clinical trial layer

The specific options available to the user depend on his role (as defined in section 5.2.3 - Use cases).

Clinical trial selection enables the options available for that clinical trial: see the volunteers enrolled in the trial (and subsequently enroll a new volunteer), go to the query management screen (where queries can be viewed, sent, answered and resolved), view or change the randomization schema for that clinical trial, go to the administrative options of the trial or simply view the trial's details.

Administration tasks over the trial include locking the trial's database, manage drug concentration information (importing and exporting) and exporting clinical trial and audit trail data. Selecting a specific volunteer from the volunteer's list will send the user to the eCRF layer.

eCRF layer

This is the intermediate layer between the clinical trial layer and the actual web interfaces where data can be entered in the database.

In the eCRF layer, information is presented to the user regarding the specific eCRF that is being visited, such as basic information about the user, the different periods of the clinical trial and events within each period, pretty much like an index of chapters and sub-chapters in a book. One interesting advantaging of the eCRF over a paper model is the possibility to include information about the current entry status of that period or event (e.g. 30% completed), to quickly inform the user about the eCRF's completeness state.

After selecting a specific event, the user will be directed to the event layer.

Event layer

This layer is composed of the interface components where users can enter data. It includes all the periods' events (such as demographics, clinical check-up or sample collection) and also the AE and clinical trial's pages.

Each component is basically a web page that enables users to enter information just as a paper page would.

5.3.2 Security and user roles

Access security was provided by ASP.Net's membership and role management frameworks.

Forms authentication method was used and usernames and passwords were stored in ASP.NET's secure fashion in the system's database. This method for web application security enables pages to be displayed differently depending on the role the authenticated user is assigned to. In this fashion, the left navigational frame of the interface (presented in Figure 10 and whose functionality is discussed in the next section) can show or hide certain menu options depending on the user's privileges. Unauthenticated users were denied access to the entire application and redirected to a login page by using ASP's security framework deny system, as shown in Figure 9 (sample of the web.config file – the configuration file of an asp.net's web application).

```
   <authorization/>

    <deny users="?"/>

</authorization>
```

Figure 9: ASP's configuration to deny anonymous user access to the site

Four different user roles were created: the monitor, investigator and system administrator were created according to the use cases presented in the previous section. Because of the small number of people involved in the management of this specific trial, the Project Manager and Data Manager roles were merged in the same interface role of the Project Manager.

A special DBMS account was created for interface access. This option was made considering the limitations of the ASP framework used. Because all interactions with the database were made through one single DBMS account, privilege management of the different user roles was controlled at the web application level. Database management privileges were managed at the DBMS level, as discussed in [25].

5.3.3 Interface layout

Figure 10 shows the actual interface layout of the EDC prototype developed. Every page in the system has the same framework and contents vary across the different pages of the system.

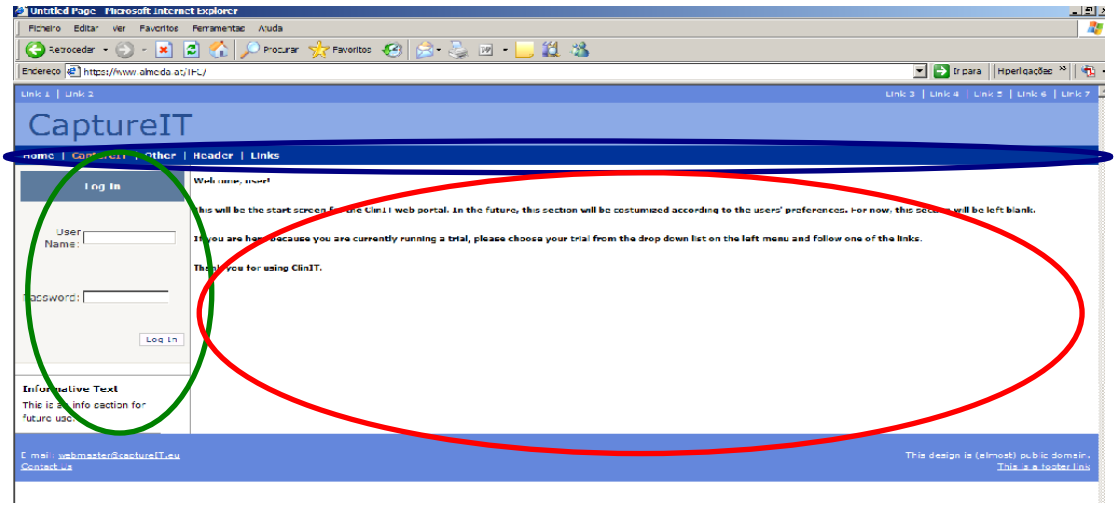


Figure 10: eCRF areas - Map Bar, Left Frame (navigation), Working Area.

The interface is composed of three main areas, highlighted in Figure 10. In the map bar the user has 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.

The left frame is where users log-in to the system. After successfully having logged in, the navigation frame will show the username of the user currently active. This navigational frame is dynamic and contents depend on the layer that the user is currently in. Its purpose is to present the user with the choices available in that specific part of the site. Figure 11 shows different aspects of the frame.

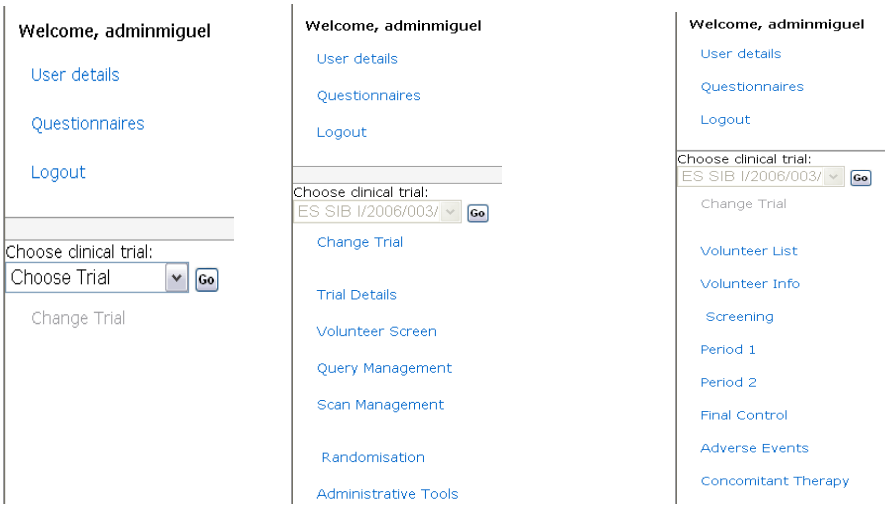


Figure 11: The navigation frame on the login layer (left), clinical trial layer (center) and eCRF layer (right)

The working area is, as the name indicates, the part of the interface where work tasks are carried out. The actual eCRF data is viewed, entered and corrected in the working area, as well as all the clinical trial related tasks – query management, source document management and trial administrative options.

The EDC system was built with the aim of being simple, straightforward and practical. The interface layout should be user friendly so that users just spend the time needed to fill the eCRF and do not lose time trying to find how the system works.

5.3.4 Events and navigation

After entering the eCRF, users can browse through its electronic pages just as they would browse pages in the paper-based method. Figure 12 shows the information available to the user once he has chosen a period of an eCRF. Notice that, as well as being able to jump to any of the tasks with a single mouse click, the user can quickly know, through means of a percentage number and a color code, the current status of every event.

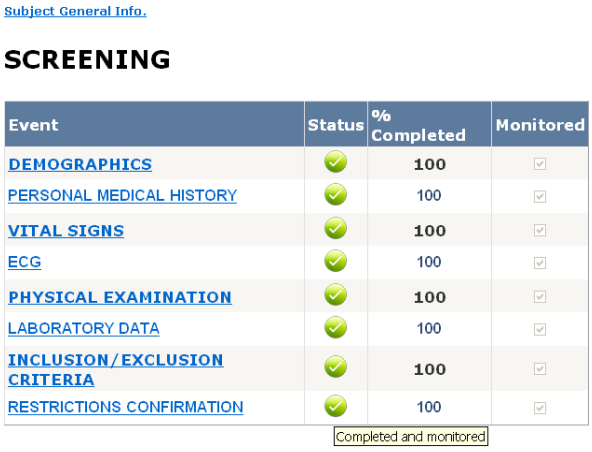


Figure 12: Task index of the Screening phase, with mouse over status and monitorization information

Selecting one of the period's tasks will send the user to the task layer. Every eCRF page has the same pattern, which is exemplified in Figure 13.

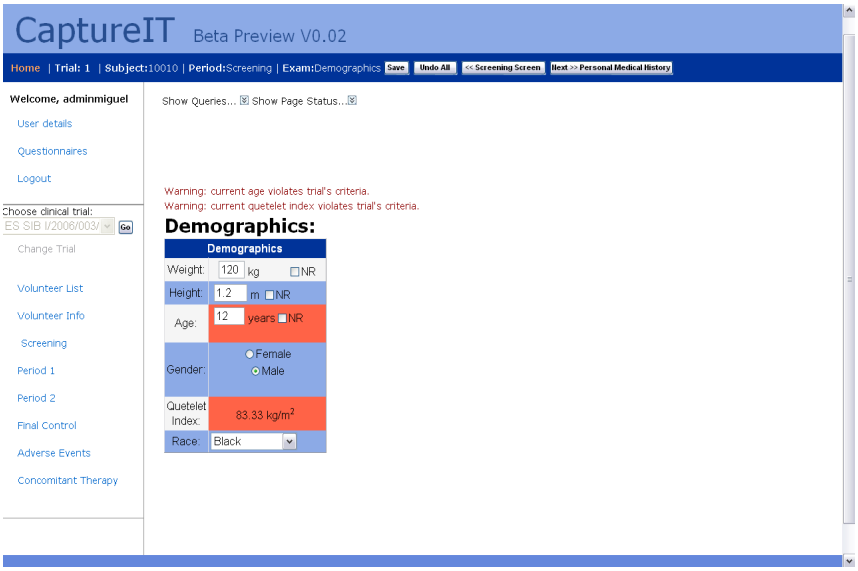


Figure 13: Demographics page (Screening). Edit checks highlight potential errors or trial violations in red

The specific forms of that event are displayed in the working area and users can enter data or change data that was previously entered if they have enough privileges to perform these actions.

To prevent typing errors from flooding the audit trail, changes are only saved in the database after the Save button (in the map bar) has been pressed. While changes have not been saved typed data has not been sent to the database and users can undo their actions by clicking the Undo button (next to the save button). This feature prevents users from accidentally changing data from the wrong subject.

Figure 13 also highlights one of the advantages of the eCRF over the traditional paper model – the edit checks. The eCRF interface's edit checks were composed of a color warning and a text warning. Whenever the specific data entered does not pass the edit check's criteria, the value in question will be highlighted in a red box so that users quickly see there is a problem with the data currently in the database. Additionally, a warning message written in dark red informs the user about the reason for that edit check. In the example shown in Figure 13, the subject's age is out of the inclusion criteria's range and the Quetelex Index is over the maximum allowed in the trial's inclusion criteria.

Although the edit checks are automatic, users can still opt not to change the values that were entered, giving the ultimate decision power investigator.

Another automatic edit check is the required field. This edit check prevents users from forgetting to fill out fields in the eCRF and, contrary to what happens with the other edit checks, it cannot be ignored by the user. In the event of the user opting not to fill out a specific value, he can either write NA (when the information is Not Applicable, such as a pregnancy test for male subjects) or NR (when data was Not Recorded for some reason). This feature can also be seen in Figure 13, where NR tick boxes are available in every field where this option is meaningful.

The edit checks also serve another purpose, which is compatibility with the database. As explained elsewhere [25], when developing the system's database, choices must be made regarding data types (e.g., age will be stored as an integer number, weight will be a real number, and dates will be stored using the Date type). Consequently, data must be sent by application server in the correct format – otherwise the database will throw an error. Edit checks are the main reason to prevent this from happening in the prototype developed. Table 14 reviews the different types of edit checks available in the interface.

Table 14: 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

To navigate along the different pages of the eCRF (as is depicted in the interface design in Annex B), the easiest way is to use the *previous* and *next* buttons available in the map bar (see Figure 13). This

option allows users to browse the eCRF in the same way they would do when flipping the pages of the paper CRF.

5.3.5 Sample collection

Each paper CRF included one page for each clinical period where investigators wrote down the sample number and collection times for each of the 23 samples (recall section 5.2.2 Clinical trial details).

One disadvantage of the paper CRF is that information is grouped by subject (each CRF has the sample collection details of one subject). In practice, investigators have to quickly collect blood samples for a considerable number of subjects in a small period of time (on each extraction time). A more practical data grouping would therefore be by collection time, i.e. reflecting real life sequence of events: each page would have sample details of *all* subjects for *each* sample collection time.

In the eCRF prototype developed this feature was introduced, as it is shown in Figure 14. Investigators can quickly change from one view to the other by pressing one button, which improves the flexibility of the process in real practice.

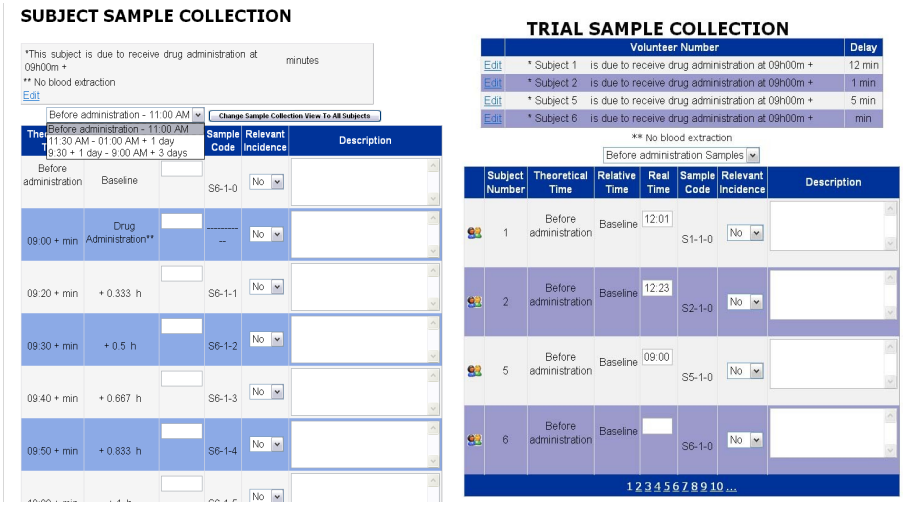


Figure 14: Sample collection views – by subject (left); by collection time (right)

5.3.6 Source documents

In section 1.1 - Clinical trial details, the paper-based method for attaching source documents to the CRF was described. Because a physical CRF is no longer present, the possibility of attaching the source documents with a staple is no longer available.

A process was developed to enable source documents addition to the database. The main idea behind this process is that documents can be converted to a digital format (such as a PDF document) that can be securely inserted in the database. Details on how this can be implemented in the database side are available in [25]. The process diagram is available in Annex C.

Random codes are generated by the database and printed on special stickers (Figure 15) that are sent to the investigation center. Because some exams (blood analyses, ECG) may have to be repeated,

special grey stickers are also available to indicate that the source document belongs to a repetition exam. The grey stickers have an additional character to indicate the number of the repetition (A is the 1st repetition, B is the 2nd repetition, etc).

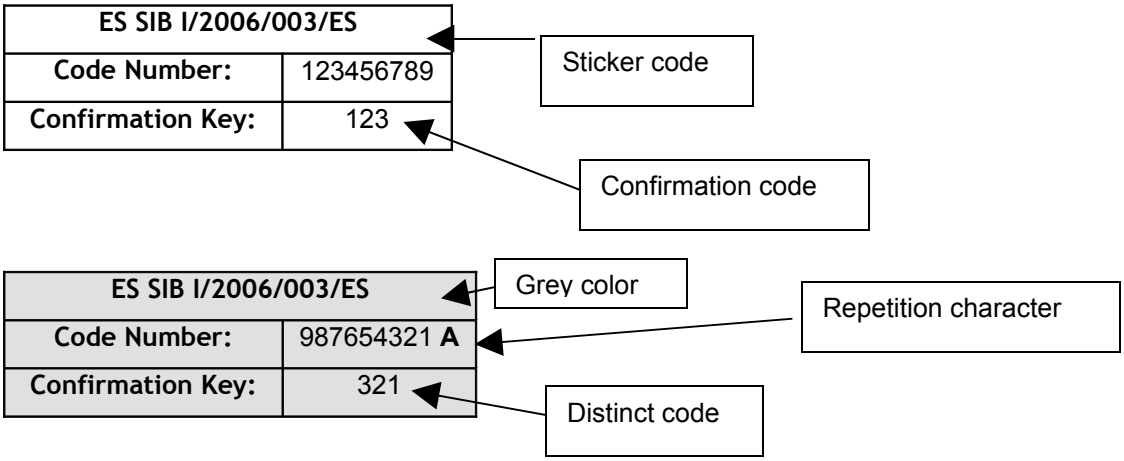


Figure 15: Example of the source document stickers – normal sticker (above) and repetition sticker (bellow)

When the investigator needed to attach a source document, he would place one unused sticker in the document. On the interface the user will choose the sticker's code number from the list of the numbers that have not been used yet (Figure 16). To reduce the possibility of error, the system will ask the user to insert a confirmation code. Validity of the pair of numbers will be given by a simple algorithm similar to a Cyclic Redundancy Code (CRC).

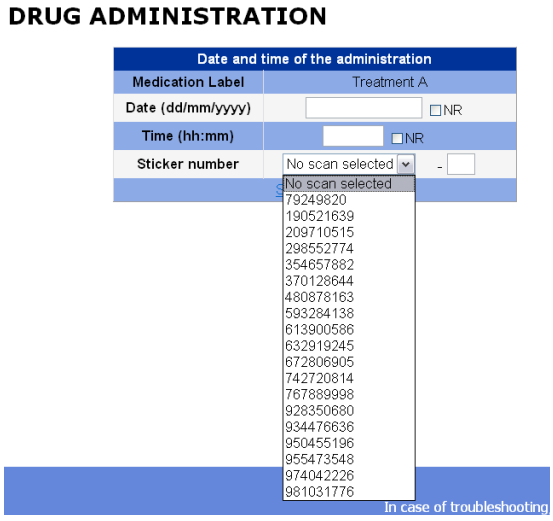


Figure 16: Example of source document attachment in the interface (in this case the administered medication's label)

Finally, source documents were sent back to the sponsor, either by fax, mail or email if they were already in an electronic format. Afterwards, the monitor would upload each electronic document to the database using an interface, by comparing the code number in the electronic document with the list of codes available in the interface. Figure 17 shows this interface, where both the upload and download documents' buttons are available to users with appropriate privileges.

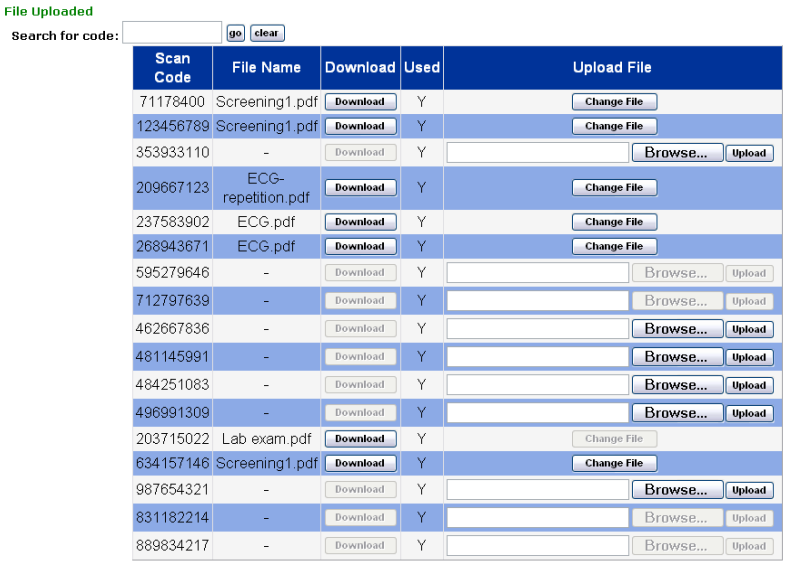


Figure 17: Source document management interface

5.3.7 e-Monitoring

Users with monitor privileges can monitor eCRF pages as soon as they are filled. On the top section of the working area of each eCRF event is an expansible menu with information about the page's current completion level and monitoring status (highlighted in Figure 18).

Pages can only be monitored after they are 100% completed, due to the fact that no entries can be left blank in the eCRF. After the page has been monitored, it becomes locked from editing to prevent further changes.

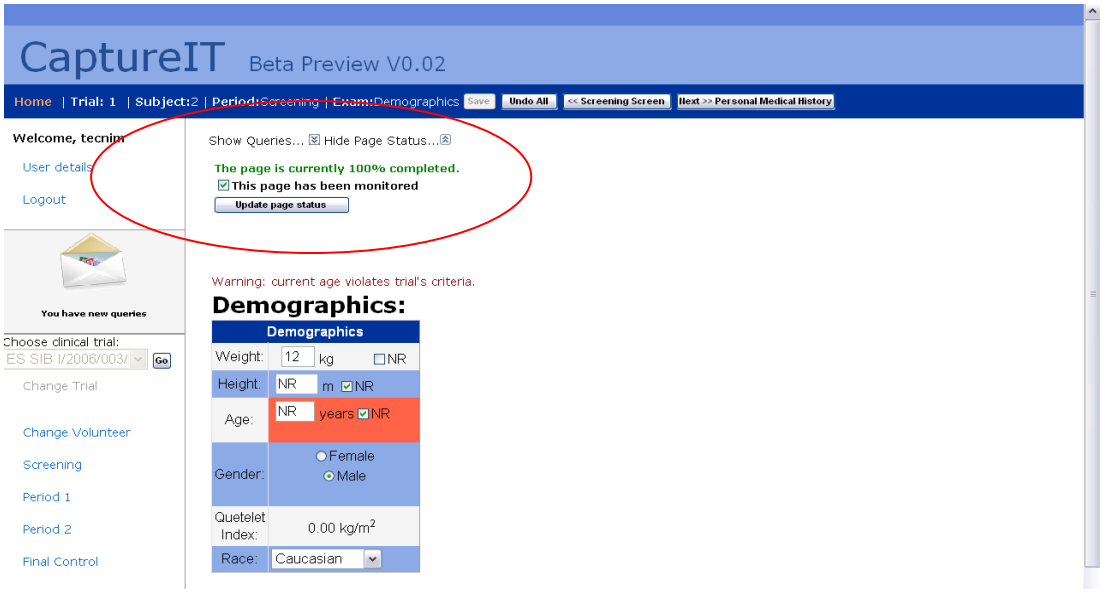


Figure 18: Monitoring area on each eCRF event page

As it has been mentioned before, this implementation allows monitors to begin their job sooner. The hierarchy level of the system enables pages to be monitored and locked individually and independently of the state of the rest of the eCRF. While in the paper-based process CRFs need to be

compiled and physically sent back to the sponsor before they can be monitored, eCRF monitoring can start immediately after data has been entered in the system.

5.3.8 Query system

Queries are sent to investigators whenever doubts arise in the process of reviewing data. The EDC prototype created has a built-in query management system to simplify interaction between the monitor who sends queries and the investigator who receives and answers them. While in the paper-based format queries are written down in a form and mailed all at once to the investigating center, e-queries are treated individually.

The query system implemented categorizes a query into one of three states: Sent (after a query is issued by the monitor), Answered (once it has been answered by the investigator) and Solved (after the monitor reads the answer and informs the system about what measures were taken given that specific answer). The process for managing a query is explained in Figure 19.

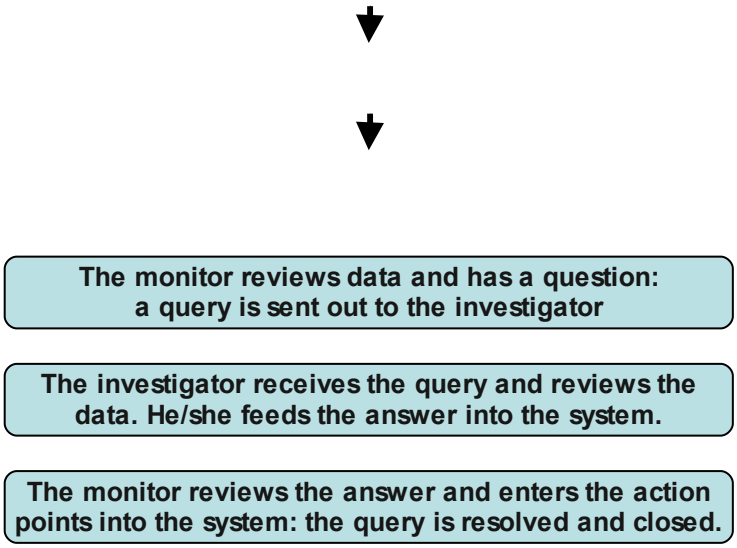


Figure 19: Process diagram for query management

Two warning systems were also implemented to inform users of new query activities. The warning system is identical for both active parties in the query process (investigators and monitors), but they are triggered on different conditions. Investigators are interested in knowing when a new query has been sent to them, so they can log into the system and answer it. Monitors are keener on being informed when an investigator has answered a query they have sent. When these actions occur, the system is triggered to send two warning messages to users. An email is sent to the user informing him of new query activity, and attaching a resume of the query in question (sender, question/answer). When the user logs into the system, and while queries remain unanswered/unsolved (for investigators/ monitors, respectively), an envelope icon is displayed in the navigation frame, along with the message “You have new queries”. This envelope message, which is linked directly to the query management screen, can be seen in Figure 18.

A list with all the queries is available in the Query Management screen (available in the clinical trial layer, see Figure 11). Monitors have access to all the queries they are monitoring, while investigators

only have access to queries sent out to their investigation center. Figure 20 highlights the working area of the query management screen. Notice that queries can be filtered to show only the answered/unanswered (for monitors/investigators, respectively).

Similarly to the monitoring expansible menu, a query menu is also available on each event's page, showing all the queries sent to a particular eCRF page of a particular user. In addition, users can immediately jump to that page from the query management screen, clicking the appropriate icon (visible in Figure 20). These features are also a flexibility improvement over the paper-based method, where investigators need to fetch that particular CRF, search for the page and finally find the field in question.

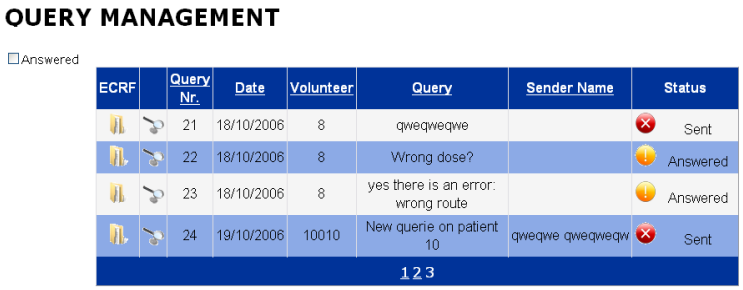


Figure 20: Query management screen listing all the queries of the clinical trial

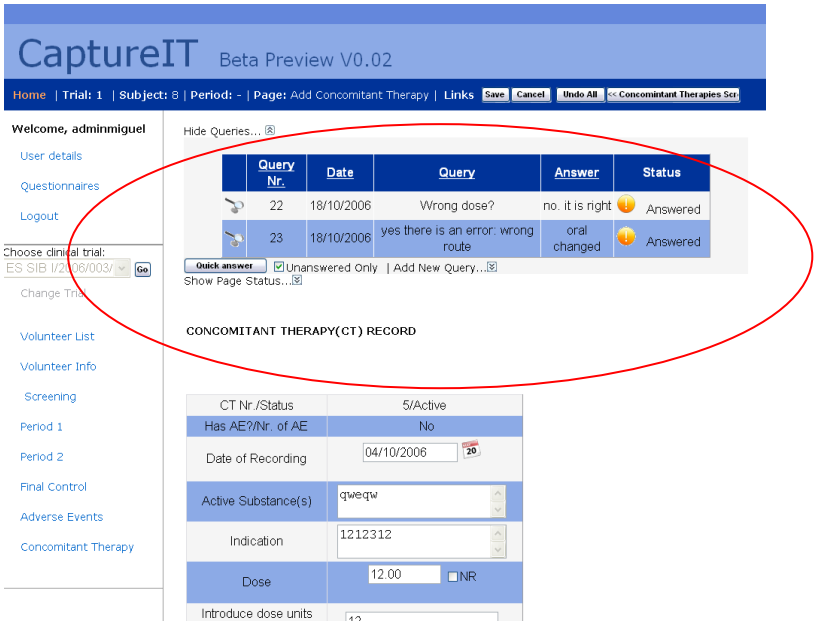


Figure 21: Query area on each eCRF event page (in the example, the CT Record). Investigators have the possibility to answer the query immediately by using the "Quick answer" button.

5.3.9 eCRF and clinical trial lock

Locking mechanisms are executed in a hierarchical way, based on the component hierarchy first mentioned in the Website navigation section.

Monitors have the responsibility to monitor each of the eCRF events, which become locked from further editing once they have been tagged as “monitored”. The eCRF lock mechanism described in section 5.2.3 - Use cases can only be finalized by the monitor once every eCRF event has been monitored, including the Concomitant Therapies and Adverse Events. This, in turn, leads to the conclusion that a clinical trial database can only be locked when all its eCRFs have been closed.

To perform the eCRF and database lock to the clinical trial, users with sufficient privileges use a specific interface in the clinical trial’s administrative tools. This interface is shown in Figure 22.

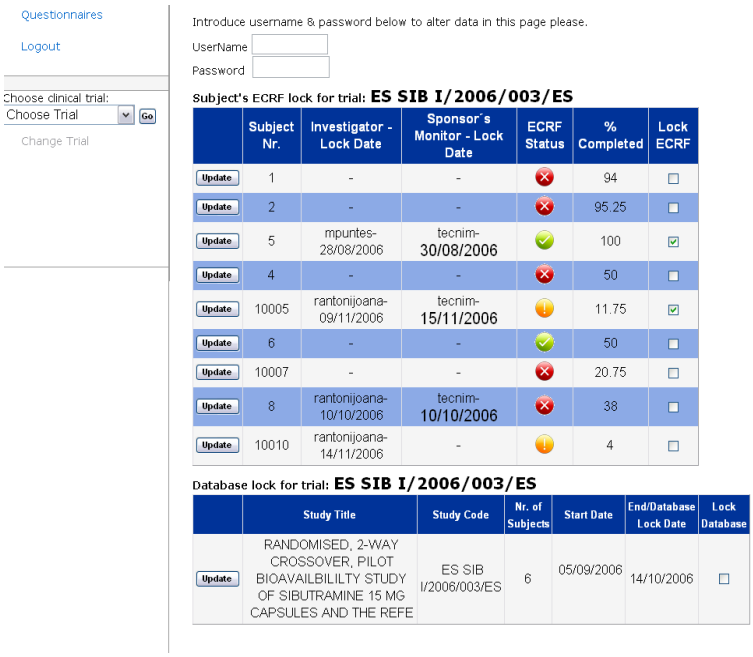


Figure 22: Overview of the eCRF and clinical trial lock interface

5.3.10Standard Operating Procedures

FDA encourages EDC system developers to establish and maintain Standard Operating Procedures (SOPs) that are pertinent to the use of the computerized system [17].

Two standard operating procedures were established during the project. The *Using the electronic case report form (eCRF)* was developed in two versions, one for investigators and one for monitors.

The FDA also requires on its CFR 21 Part 11 that users of electronic systems have the education, training and experience to perform their assigned tasks [15]. This is also referenced in [17] (in chapter X – Training of personnel). Practical training sessions were conducted on site to system users to teach them how to use the system. Table 15 lists the three training sessions conducted.

Table 15: EDC system’s training sessions

Location	Description	# Participants	Duration (hours)
Lisbon	Training session focused on the monitor and project manager’s work	4	2
Barcelona	Training session focused on the investigator’s work	6	2
Barcelona	Training session focused on the investigator’s work	1	1.5

5.4 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 (Table 16). 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.

5.4.1 Time between the beginning and end of the project

This indicator measures the sum of the three periods mentioned.

5.4.2 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. The clinical trial start date, last clinical procedure and the database lock considered were extracted from the EDC database using SQL statements on the audit trail system.

Table 16: Tasks in the three main periods of time of the clinical trial process

	Pre-trial period	Clinical trial period	Post trial period
Paper process	CRF creation; Final database creation	Data entry	Data review and query issuing; Double data entry Data crosschecking and database lock
EDC	EDC system creation	Data entry	Data review and query issuing; Database lock

5.4.3 Average response time

This indicator measures 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.

For the EDC system, retrieving this information is straightforward: the system records every date of query activity – send date, answer date and solve date. An appropriate SQL statement was built to export this information and calculate the average response time of the EDC system.

The response time was not available for the paper-based process. Historical data from a previous multi-center study conducted by DMED/GT was used instead [26]. For the comparison to be valid, it has to be assumed that all investigators have the same response awareness to queries, i.e. the willingness to respond to a query when it arrives must be the same.

5.5 Quality indicators

In order to retrieve feedback from the prototype system's users, two online questionnaires were conducted. The transcription error rate and number of queries were also measured.

5.5.1 Perceived usefulness and ease of use questionnaire

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 (as detailed in the Standard Operating Procedures' section). After the training session, users were asked to answer an online questionnaire available in the Questionnaire Center (Figure 23).

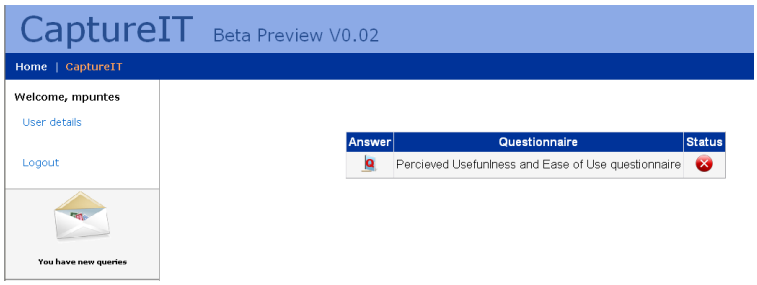


Figure 23: Overview of the questionnaire center, with information and link regarding the questionnaires sent out to the user

The questionnaire consisted of fifteen questions: three of them were aimed at characterizing users on their prior experience with computers and EDC systems; six were aimed at evaluating users' perceived usefulness and the remaining six questions aimed at evaluating users' perceived ease of use. The questionnaire asked participants to rate the extent to which they agreed with each statement, using a 7 point Likert scale (with extreme values being Unlikely – Likely). Users were also invited to leave comments whenever they found them appropriate. The questionnaire was developed and validated by [27]. Reliability of the questionnaire results was given by Cronbach alpha, which is a measure how well a set of items measures a single unidimensional latent construct. Test validity was assessed by factor analyzing the 12 scale items using principal components extraction and oblique rotation, in the same fashion as in [27] and further explained in [28]. Two factors were extracted, corresponding to the two concepts of the study (usefulness and ease of use). Statistical analysis was carried out using SPSS 11.0 (SPSS Inc.).

Table 17: Online questionnaires

Conditions	Variables measured	# Answers
Users were trained to use the system and performed basic tasks in 2 hour group training sessions	Perceived usefulness and ease of use	8
Questionnaire was answered after extensive system usage	User satisfaction of the human-computer interface	8

5.5.2 User satisfaction of the human-computer interface

The second questionnaire was conducted after the clinical trial ended and users worked with the system extensively. The main objective of this questionnaire was to ascertain how satisfied users were with the interface created for the EDC prototype. Access to the questionnaire was made in the same fashion as in the first questionnaire.

A Generic User Interface Questionnaire (QUIS) was used – version 5.0 of the QUIS developed by J. Chin of the University of Maryland's Department of Psychology [29]. Version 5.0 consists of a 27 Likert like questions that ask users to evaluate the interface on five sets of characteristics: overall reaction to the system; screen; terminology and system information; learning; system capabilities. This version of the questionnaire has a high degree of reliability (Cronbach's alpha of 0.939) and good correspondence of learning and terminology sections and its latent factors. Additionally, users were invited to list the three most positive and negative aspects of the system. Annex H shows a printed version of the questionnaire sent out to users.

5.5.3 Transcription error rate and number of queries

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. The crosschecking process is aimed at comparing data entered independently and catching the possible transcription errors. After this process is completed, transcription errors that are not caught will remain in the system.

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 of DMED/GT and data from that sample was transcribed by two users independently. This sample consisted of pages 3, 4, 13, 14, 16 and 17 of the CRF, in a total of 1692 fields. The sample is assumed to be representative of the complete CRF. The total number of fields in the CRF is 2460. 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.

5.6 Validation definition in EDC systems

5.6.1 Determination of the life-cycle phase the software is currently in

The DMED/GT Pharmacovigilance Database is a system developed in Microsoft Access (Microsoft Corporation) in the early 2000's. It is currently in use and has around 150 adverse events and adverse reactions that were received by Grupo Tecnimede in the last decade.

The V model is a variation of the waterfall model for software development [23] that demonstrates how the testing activities are related with the system's analysis and design.

Taken this model into consideration, the Phamacovigilance Database was already accepted and is currently in operation. It is subject to corrective and perfective maintenance, the last of which was done in the beginning of 2008.

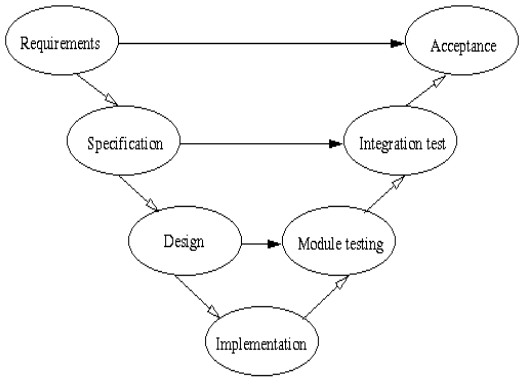


Figure 24: The V model

5.6.2 Determination of the level of validation that is necessary for the system

The level of validation that is necessary for computerized systems in regulated environments depends on variables such as the potential harm to human health or human life, the expected frequency of use or the previous inspections it has received - it should be noted that the system may have already been inspected by regulatory authorities. Moreover, in the event of a system that was developed by a third party, some sort of validation may have already been performed by the vendor. In this case, the company should audit its vendor to ensure the validation activities are considered to be sufficient for that system.

Taking into consideration the V model for software development, a parallelism can be made between the testing activities on the right hand side of the model and the validation process (Table 18).

Table 18: Parallelism between V model's testing activities and validation activities

V model activity	Validation activities
Coding	Validate individual code and units of code
Unit & integration testing	Validate units of code (such as libraries and packages that perform individual functions) Validate unit integration
System testing	System validation, including integration with operating system, hardware and network Verify system design
Acceptance testing	User acceptance validation Ensure all system requirements are met
Operation & Maintenance	Plan that addresses maintenance and future changes

The validation of individual code (e.g. functions/methods in a programming language like C or Java), combined with the validation of units of code that perform a specific activity should ensure that the function is working correctly, i.e., that specific inputs will produce predictable outputs. Validation activities should also encompass error and stress testing. Interestingly, the FDA comments that “a successful test is one that finds an error” [18].

The integration with the remaining parts of the system is also important when validating software. The validation responsible should ensure the software integrates with the operating system, the specific hardware where it has been deployed and the network system the hardware is connected to.

The verification that the software is performing according to its requirements is, as referred, crucial in the validation process, and it is part of the acceptance testing activities in the V model. Ensuring that the users know how to operate with the system – the user acceptance validation activity – is also important, as inadequate training of personnel is a potential cause of validation failure [18], [36].

Lastly, validation should also cover the last step in the V model – the operation and maintenance. The formal definition of the procedure in case of change is important. Between 1992 and 1998, 79% of software related recalls made by the FDA were caused by software defects introduced when changes were made to the software after its initial production and distribution [18].

In order to assess the level of risk inherent to the use of this system, and therefore determine the extent of validation necessary for this system, a risk assessment score system was used. This score card takes into account previous industry and regulatory authorities' validation of system, CFR Part 11 compliance, expected frequency of use and potential harm to human life in the event of system failure. Table 19 exemplifies some items of interest to the validation responsible when determining the level of risk associated with the software.

Table 19: Items of interest in the determination of the software's risk (based on [30] and [31])

Item	Test	Pharmacovigilance db
Regulatory experience	To test if the system has already been subject to an audit by either regulatory agencies or external companies.	No audit performed

GXP requirements	To test if the type of data managed by the system is covered by any Good Practice guide	Covered by GXP
Impact of data errors/corruption	Assess the impact that the loss of data has on the process	High impact on data quality
CFR 21 Part 11 Compliance	Determine if the system is compliant with FDA's CFR Part 11	Not Part 11 compliant
System use in the industry	Determine if the system is or is not widely used by other companies	Custom system, not used outside the company
Frequency of use	Determine the estimated frequency of use of the system	Weekly
Impact of unavailability on user's tasks	Assess the criticality of the system to people's tasks and whether or not alternative processes for the execution of these tasks are in place	People cannot perform the task if the system is unavailable
Life span of the system	Expected life span of the system	Years (more than 3)
Impact on human health and life	Determine the impact of a system malfunction on the user or patients' life or health	No impact

The last row categorizes the Pharmacovigilance Database according to these items. Based on these findings, a recommendation was made that all system's functionalities should be subject to validation activities. Given the fact that it is a legacy system, validation activities were restricted to operational validation. Because the database has been in use for several years, a retrospective validation protocol was also planned. This is also in accordance with the FDA's recommendations on how to proceed in the validation of database software, where the validation auditor should perform functional testing (using test data sets) and research for limitation, problems and defect corrections in the software [17].

5.6.3 Definition and execution of a validation plan

The validation plan describes the measures and responsibilities agreed by the validation planning staff. All those involved in the software process should be part of this staff, from IT and development personnel to system users. In the Pharmacovigilance Database tested, the panel consisted of Augusto Filipe, MD (Head of Medical Department and Qualified Person for Pharmacovigilance - QPPV), Ana Tomé, PharmD (Deputy of the QPPV and system user) and Miguel Almeida (head of the independent validation process). The validation plan also lists all the assumptions about the limitations on the extent of validation and gives justification for any exclusions [36].

The contents of the validation plan and the activities that it will enlist naturally depends on the findings of the previous steps. It is, however, essential for the validation process that the plan contains – or points to – the system business and functional requirements. The risk assessment activities that were conducted should also be listed in the validation plan.

The combination of the limitations and extension of the validation effort described in the plan, a list with all the tasks and responsibilities should be produced. Each task should be correlated with one or more tests in the Test Plan document (described later).

Accountability is very important in the validation activities. A potential cause of software validation failure is the lack of evidence of review and approval of documentation by qualified staff [36]. The validation plan should therefore be signed by qualified staff, and each change in the version of the document should also be registered.

For any validation process conducted in a regulated environment , a validation plan should therefore have the contents listed in Table 20

Table 20: 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

The rest of the chapter is dedicated to the definition of the validation plan contents.

5.7 Version Control and Plan Approval

A document control sheet was developed to register the changes made between versions of the plan. For each version number, the section(s) changed are listed and a summary of changes is written. The date of the change is also registered. Table 21 shows the heading of the version control table.

Table 21: Version control heading

Version No.	Effective Date	Section changed	Change Summary

The plan approval was implemented as a sheet that contains information about the qualified personnel that approved the current version of the document. For each version of the Validation Plan a new plan approval sheet should be created. The document's name, title and version are shown in the page, as well as the identification of the personnel that signed the test plan (and its respective signature), as shown in Table 22.

Table 22: Information and signatures of the signataries of the Validation Plan

Company	Name	Job Title	Date	Signature

5.8 Objectives

The validation plan was developed for the software entitled "*Aplicação de registo de acontecimentos e reacções adversas*" (referred as Pharmacovigilance Database), version DI/2.00.

The *objectives* section defined the purpose of the validation, namely:

1) To evaluate the system's ability to properly perform its intended functions;
2) To evaluate the ability of the users to understand and correctly interface with it.

All tests conducted in the validation process were be recorded to demonstrate the evaluation.

5.9 System description

The Pharmacovigilance Database is a database developed in Microsoft Access (Microsoft Corporation) and consists of a single database file named *ARA_database.db*. Its objective is to serve as a repository for the information that Grupo Tecnimede receives regarding SARs of its products.

The Pharmacovigilance Database allows users to record, edit and delete adverse events. It also allows users to query the database to retrieve a list of SARs grouped by year, by product and by system order class (SOC). Reports can also be generated. Table 23 summarizes the database functions available to the user.

The system can be broken down into two components:

1. Microsoft Access database tables
2. Microsoft Access forms to interface with the tables

The database is stored in a data server in the company network and is accessed by users on remote computers inside DMED/GT's network.

Table 23: Database functions and description.

Function	Description
Save Adverse event	Allows users to create an adverse event and store it on the database
Edit Adverse event	Allows users to edit an already created adverse event
Query Adverse events	Query the database to show AEs grouped/filtered by:

	– product – SOC – Seriousness – Predictability – Causality – Source – Notifier
Report generation	Generate query reports, which can be printed. Reports can be grouped/filtered by: – Product – SOC – Seriousness – Predictability – Causality

Due to the architecture of MS Access databases, computers which access the Pharmacovigilance Database (clients) must have MS Access installed. The minimum system requirements for running this software are, according to the manufacturer [32]:

System requirements (MS Access 2003)

Microsoft Windows Operating System (Windows 2000 or above)

Computer with Pentium 133 megahertz (MHz) or higher processor; Pentium III recommended

RAM: 64 MB (Windows 2000), 128 MB (Windows XP)

300 MB hard disk space for MS Access

Due to the remote location of the Database, clients must have a network connection and privileges to access the directory where the database resides in the server computer.

Although the system had been in use in DMED/GT for several years, no documentation had ever been created. The System Requirements, which were already referred to as essential to the validation activity, were not available. As part of the validation process, the system's User Requirements were defined and are listed in Table 24.

Table 24: User requirements definition for the Pharmacovigillance Database

User requirements
1. Ability to register AEs and Adverse Reactions (ARs) in the database. The origin of these events can be: ● Competent Authority (AR - Autoridade Regulamentar);

• Healthcare Professional (ES - Espontâneo/Spontaneous); • Clinical Trials (EC - Estudos Clínicos); • Patient/Consumer (CO - Consumidor); • Literature (LT – Literatura).
2. Ability to view inserted entries
3. Availability to Tecnimede's Medical Department Staff. Only one user shall access the database at a time.
4. Weighted error frequency of less than 5%
5. Missing value frequency of less than 2%
6. Possibility to query the database to retrieve listings of events during a period of time.
7. Possibility to export query listings.
8. Information should be backed up at least once every week.
9. Information should not be edited by unauthorized personnel

Error and missing value definition

For the successful evaluation of requirements 4 and 5, there should be a clear definition of what constitutes an error and a missing value in the context of the software. Table 24 is a guideline of what should constitute an error between the source document and the database repository.

Table 25: Definition of what constitutes an error in the database

Field type	Strategy	Equality example	Error example
Codes	Codes should be exactly equal. Any change in the string should constitute an error	001/99/EC = 001/99/EC	001/99/EC != 001-99-EC != 0001/99/EC != 001/99/ec
Exclusively numeric fields	Value should be the same.	1 = 1 01 = 1	22,5 != 22,45
Dates	Day, month and year should be equal	1999/12/31 = 1999-12-31	1999/12/31 != 1999/12/30
Multiple choice	Selected choice should be the same	Option 1 = Option 1	Option 1 != Option 2
Open text	Meaning of text should be the same	“Subject is male” = “Male”	“BP within normal values” != “BP in abnormal values”

For the purposes of the pharmacovigilance software, an omission was defined as a missing value in the database. For an omission to exist, two events must occur simultaneously: 1) There is a blank field in the Pharmacovigilance Database; 2) The information regarding that field is available in the source documents.

Weighted frequencies

The minimum information required to notify a SAR is, according to [33]: a) an identifiable patient (initials, age or sex); b) an identifiable reporter, which should be a healthcare professional; c) a suspected medicinal product; d) a suspected SAR.

It should follow that the information concerning these items should be regarded essential for the existence of an SAR record, while the remaining fields are extra information to complement the record.

A weight system was developed to reflect this relative importance of the different fields in the database. For the determination of the weight for each field, three specialists were independently consulted and the results were averages. The final weights are listed in Table 26.

Table 26: Error weights for database fields

Field	weight (ρ)
AE code (GTM)	3
Patient's initials	3
Patient's age	3
Patient's sex	3
MedDRA code	4
Notifier	2
Product	6
Remaining fields	1

Weighted error frequency and missing value frequency were calculated using the formulas:

$$\frac{\sum(error \times \rho)}{\sum(fields)} \qquad \frac{\sum(missing \times \rho)}{\sum(fields)}$$

where ρ is the weight of that particular field.

5.10 Risk assessment

This section of the validation plan provided information about the identifiable risks to the system and how they are addressed by the plan. Table 27 lists these findings.

For each identifiable risk to the system – and the entire operational process – a task should provide assurance that the risk has been minimized. The tasks are described in the next section.

Table 27: Identifiable risks and addressing strategies

Risk	Addressing strategy
Users unable to understand how to use the system	Check SOPs
System's data does not reflect reality	Check for errors. Test CRUD functions
System's characteristics are changed (eg: change data type)	Check system access Check SOPs
Security risks (database deletion, access control, crud operations)	Check system access Check backup strategy

5.11 Scope

This section describes the extent of the validation exercise that was conducted.

5.11.1 Constraints on the validation activities

Due to the fact that it has been delivered and is in operation, the Pharmacovigilance Database is categorized as an in-house legacy system. This, together with the risk analysis result, determines that validation activities were restricted to:

1. Operational validation of the user interface
2. Security and permission policies on the system
3. Performance and load testing
4. Failure mitigation strategies

5.11.2 Assumptions for successful execution of the Validation Plan

Operational validation of functions concerning CRUD (create, read, update and delete) operations of SARs requires the identification of all editable fields in the system and what the boundary values for what is considered normal operation are. The list of all editable fields, their types and stress conditions can be found in Annex D.

5.11.3 Boundaries to the validation activities

Open text fields were not be compared by string equality, but by meaning, as described in Table 25. Two reasons were behind this decision. Firstly, large strings like sentences and paragraphs are likely to have differences that do not alter the meaning of the field (commas, semicolons, capital letters): the consideration of these differences as errors would contaminate the notion of “error frequency”. Secondly, some fields on the database are not directly related to a field in the source documents. This

is especially true in literature AEs, where the user has to search a full text to fill out the database form. Direct string comparison would be impossible to assess in these situations.

Whenever doubt arises as to assess equality between source documents and database fields, two independent, experienced professionals were consulted.

There is an infinite number of stress conditions that can be posed to the system, and a complete validation of all possible stress values would be impossible. Stress conditions are defined in Annex D. A test set representative of stress conditions was defined by a panel of experts and the set was used to test stress conditions.

5.12 Exclusions within the scope

MedDRA - the Medical Dictionary for Regulatory Activities - is a medically valid terminology developed by the ICH with an emphasis on ease of use for data entry, retrieval, analysis, and display, as well as a suitable balance between sensitivity and specificity within the regulatory environment. MedDRA codes are used in the Pharmacovigilance Database to characterize the SARs. Because MedDRA codes are revised twice a year (in March and September), it is possible that codes, terms or SOCs entered in the system in the past were changed or deleted. It was therefore not possible to retrospectively determine errors on MedDRA related fields. A prospective error frequency calculation was performed for MedDRA related fields.

The prospective error frequency calculation was done by choosing a representative sample of the database and re-introducing the MedDRA related fields on a clean database, using the latest MedDRA version available. To calculate the sample size, it was assumed that the probability of error of inserting a field in the database followed a normal distribution. The number *N* of SARs on the database is 149. For a margin of error *E* of 5% and for a confidence level *c* of 95%, assuming the expected probability of error *r* of 10%, the sample size *n* should be, according to the formula, 72 cases.

$$n = \frac{N \times x}{((N-1) \times E^2 + x)} \qquad x = Z\left(\frac{c}{100}\right)^2 r(100-r)$$

Figure 25: Sample size calculation

5.13 Tasks and responsibilities

This section of the validation plan lists the tasks that were agreed to be performed as part of the validation of the Pharmacovigilance Database. Table 28 shows the tasks that were performed in the validation, as well as the traceability matrix created. The purpose of a traceability matrix is to show the coverage of testing or verification against a specific requirement [34]. In this case, the traceability matrix was implemented by adding two columns to the tasks' table, one identifying the test(s) that were performed for each task and the other identifying which requirement that test covered (recall Table 24 - User requirements definition for the Pharmacovigillance Database).

Table 28 - Tasks and responsibilities.

Task	Description	Document	Responsible	Test plan	Requirement #

		reference			
Error frequency	Determine the weighted error frequency of the AEs in the database	Requirements: What constitutes error		Test Case 9	4
Retrospective missing values frequency	Determine the missing values' frequency in the database	Requirements: What constitutes a missing value		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

Every column in Table 28 is self-explanatory. The “document reference” column identifies other documents that have important information regarding that specific task. The “responsible” column should be signed by the person who leads that task.

5.13.1 Test plan

Table 28 refers 9 test cases that were written as part of the validation process. These test cases are commonly compiled in another document called the Test Plan.

It would be cumbersome to detail every Test Case in this section. As an alternative, the prototype of the Test Case developed is shown, and Table 31 summarizes all the test cases that were developed. The complete Test Plan can be found in Annex E.

5.13.2 Test Case Prototype

Each test case has a title and four sections – its objective, the requirements, the test procedure and the acceptance criteria. For each section, the contents of Test Case 1 are shown for exemplification.

Objective

The objective is a short statement of the objective of the test case (similar to the “description” column of Table 28). For Test Case 1 (entitled *Function: Save*), the objective is:

Assess the Save function of the software with normal values. This function allows a user to register a new SAR in the database.

Test requirements

The requirements are summarized in a table and represent the pre-requisites necessary for the test to be performed. Requirements can vary in type: an *input data* requirement means the test requires some sort of input (for example, an input file or a set of written data); a *previous test* requirement means that another test should have been performed before an attempt to execute that test. Requirements are listed in a table equal to the one presented in Table 29 (which exemplifies the requirements of Test Case 1).

Table 29: Requirements table

Requirement type	Description	Documents/data
Input data	Information of the AE which will be inserted on the database	Input data 1

Test Procedure

The sequence of steps necessary for the execution of the test are detailed in the test procedure. A detail explanation of all the steps necessary to perform the test is very important to guarantee reproducibility of the test. Table 30 shows the template for the test procedure description, filled with the example data taken from Test Case 1.

Table 30: Test procedure

Step	Screen	Action
1.	None	Open the database
2.	Main Menu	Choose “Insert new AE”
3.	AE Form	Insert data as defined in “Input data 1”
4.	AE Form	Click save button
5.	Main Menu	Query database by inserted AE's code

Acceptance criteria

The acceptance criteria should be an objective and concise set of events that must be met at the end of the test for it to be considered a success. It should be noted that an acceptance criterion may not always be an absence of errors. For example, if the the software was design to yield an error if the user inputs an invalid field, the successful test should precisely be the existence of the corresponding error message. For Test Case 1, the acceptance criteria are:

Suspected Adverse Event is inserted in the database. Last step should yield a screen with the new SAR. Test is passed if and only if the information is identical to the input data.

The summary of all the test cases developed as part of the validation process for the Pharmacovigilance Database is shown below.

Table 31: Summary of the test cases created as part of the validation process

Test Case	Objectives	Requirements	Acceptance criteria
Test Case 1 – Function: Save	Assess the Save function of the software with normal values. This function allows a user to register a new AE in the database.	Input data set 1	Adverse Event is inserted in the database. Last step should yield a screen with the new AE. Test is passed if and only if the information is identical to the input data.
Test Case 2 – Function: Edit	Assess the Edit function of the software. This function allows a user to change information of an existing AE in the database.	Input data set 2 At least one AE should be already present in the database	Adverse Event is changed in the database. Last step should yield a screen with the AE. Test is passed if and only if the information is identical to the input data.
Test Case 3 – Function: Query	Evaluate the query functions of the software. This function allows a user to query the database and retrieve listings of the entries, filtered and ordered by various fields.	Test Case 1 Test Case 2 Input data set 1 Input data set 2 Input data set 3	Each query should produce a list of items of a size N + 1, where N is the number of events on the database before test case 1 that pass the query filter and 1 corresponds to the AE inserted in test case 1. Because Input data 3 should be distinct, this adverse event should not be shown on any of the lists, except the queries produced in step 8. The result of the queries produced in step 8 should be a list of items of size N + 2.
Test Case 4 – Function: Report	Evaluate the report functions of the software. This function allows a user to query the database and print a report of the listings produced, filtered and ordered by various fields.	Test Case 1 Test Case 2 Input data set 1 Input data set 2 Input data set 3	Each query should produce an exportable report of size N + 1, where N is the number of events on the database before test case 1 that pass the query filter and 1 corresponds to the AE inserted in test case 1. Because Input data 3 should be distinct, this adverse event should not be shown on any of the reports, except the reports produced in step 8.The result should have a size of N + 2. Exportable reports should be confirmed either by printing or by the production of a PDF.
Test Case 5 - Stress testing of Function: Save	Assess the Save function of the software with stress conditions.	Input data set 4	Adverse Event is inserted in the database. If insertion is rejected due to impossible values or wrong data, the tester should correct the impossible/wrong format values and try to insert the AE again. Last step should yield a screen with the new AE. Test is passed if and only if the information is identical to the input data.

Test Case 6 – Backup procedure	Assess the backup procedure is in accordance with software specification.		Last backup should be one week old or newer. Backup procedure should be configured to back up the database at least once every week.
Test Case 7 – Access control	Assess the access control policy implemented and ensure only authorized users have edit privileges in the database.	Input data set 1 At least one AE should be already present in the database	Test is passed if and only if: 1. The AE in step 2 is not successfully inserted on the database 2. The field “Observações” is not successfully changed in step 4.
Test Case 8 – Weighted missing values' frequency	To determine the weighted missing values' frequency of the fields in the database.		Test is passed if and only if weighted missing values frequency is less than what defined in the Requirements documentation.
Test Case 9 – Weighted error frequency	To determine the weighted error frequency of the fields in the database.		Test is passed if and only if weighted error frequency is less than what defined in the Requirements documentation.

6 Results

6.1 Performance indicators

6.1.1 Time between the beginning and end of the project and time from last clinical activity to database lock

Clinical trial activities were considered the same for both systems and lasted a total of 37 days.

The EDC project began in March and ended on October 26th. The estimated number of working days that were necessary to build the system was 163. A 10% error margin (16.3 days) should be included in this estimate, to take into account periods of time where developers did not work on this project for various reasons. This time takes into account the entire process necessary to build the system: bibliographic research, learning of the application layer's programming language, design and implementation of the system. Also included in this value is the development time of benchmarking tools, such as the questionnaire center.

In the EDC system, the last query was resolved on November 17th, 37 days after the last clinical activity. The eCRFs were locked 5 days later and the database was closed 60 days after the last clinical activity. Because no relevant activity was registered between eCRF and database lock, and because the 5 day difference between the last query resolution and eCRF was due to the monitor's lack of experience with the EDC SOP, the database was ready for lock on October 17th. As the increased time was attributable not to the system's performance but to SOP interpretation, the date of October 17th was chosen as the end of the project and consequently the database lock date.

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. Therefore, 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 paper CRF took 16 hours (2 work days) to elaborate, and this task was performed by experienced industry users.

The transcription and crosschecking times were measured when the sampled CRF was transcribed. Assuming the sample is representative, the total times for these tasks are listed in Table 32. Single data entry time is the average entry time for both operators who entered data. Double data entry time is the sum of both user's entry times (1 hour each) and the crosschecking time to achieve consistency between the two databases (4 hours). This would be the theoretical transcription time. In the clinical trial study, the transcription process took a total of 27 days.

Database closure time for the paper process was on November 30th, 50 days after the last clinical trial activity.

Table 32: Single and double data entry times for the CRF in the transcription process

Metric	Paper process (hours)

Theoretical single data entry time	1
Theoretical double data entry time	8
Study's double data entry time	27 days

The database creation time at the AIF-HSCSP site was estimated to be 0.5 days. Table 33 summarizes the times recorded and lists the performance indicators measured.

Table 33: Summary of time indicators of both systems (time estimative in days[1])

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

6.1.2 Average query response time

The average query response time for the EDC process was 2.8 ± 2.6 days. The 35 queries issued were analyzed; only full days were considered and weekends were not removed when determining the average response time.

In the historical control used to determine query response times in the paper process, five query batches were issued. Table 34 lists the number of queries sent out to each center on each of the issuing batches and the time (in days) until queries were answered back.

Table 34: Queries issued in the paper-based study to the eight centers (N= number of queries, days = days until query was answered)

	1st issuing		2nd issuing		3rd issuing		4th issuing		5th issuing	
	N	days	N	days	N	days	n	days	N	days
C1					174	87	24	14	6	3
C2	25	18			85	9	9	15	3	8
C3	50	42	4	9	16	39				
C4					115	16	26	9	5	5
C5	76	14	9	66	73	42	3	16	1	3
C6	77	191	1	106	72	45	6	22	8	10
C7	28	45			101	35	15	8	2	9
C8					1	42				

The average query response time in the paper trial was 49 ± 48 days.

[1] For paper's CRF and database creation, each day corresponds to a normal, 8 hour labor day. Weekends were excluded in the pre-clinical period and included in clinical and post-clinical periods

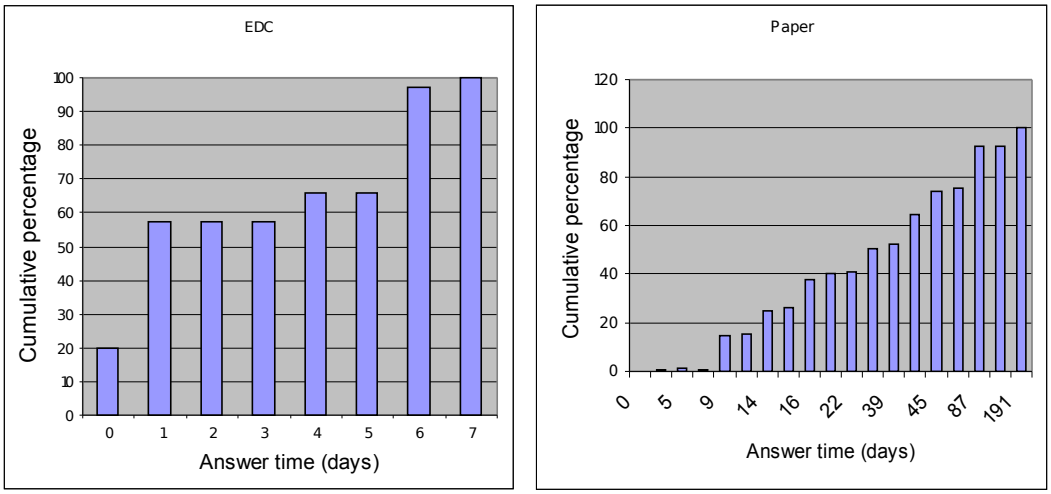


Figure 26: Cumulative percentage of the query answer time in days – EDC process (left) and paper process (right)

Figure 26 presents the cumulative percentage of query answer time. While 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, 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.

Figure 27 shows the average query time histograms for the EDC and paper based processes. While in EDC all queries are resolved within one week, in the paper based benchmark there is a significant number of queries resolved months after they have been issued (notice the frequency of 87 days and 191 days).

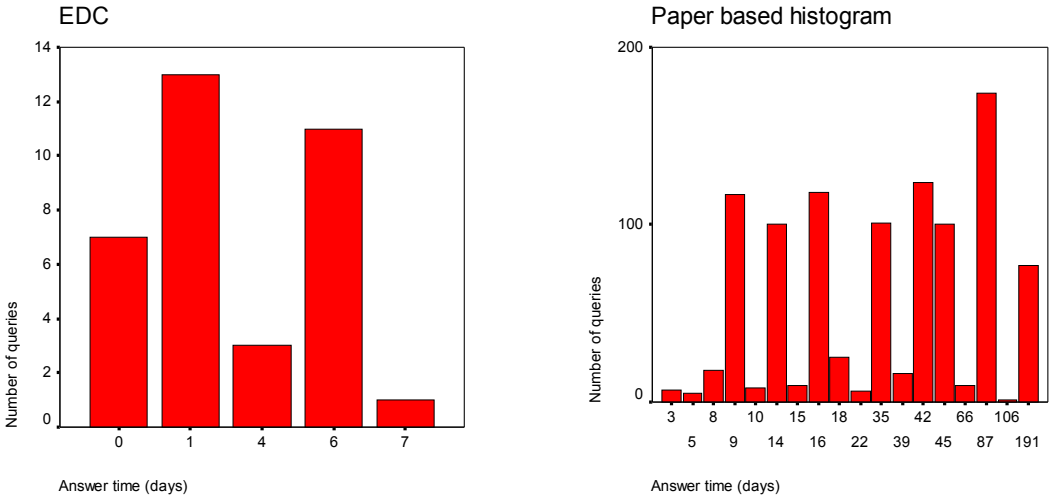


Figure 27: Average query answer time histogram – EDC (left) and paper process (right)

Regarding the distribution of the monitor's work through the post clinical period, nearly half (48%) of the queries were issued in the same day (19-10-2006) and 73% of the queries were issued in two

days (13-10-2006 and 19-10-2006). The investigator answered 79% of the queries in one day – 20-10-2006 - and 88% were answered in two days (20-10-2006 and 6-11-2006).

6.2 Quality indicators

6.2.1 Users' perceived usefulness and ease of use of the system

The eight users who answered the questionnaire were characterized on their computer use habits. 67% of the users were either very experienced or experienced computer users and 72% referred they had no or very little experience in using EDC systems. All the users have a very frequent or frequent usage of computers. Figure 28 graphically shows these results.

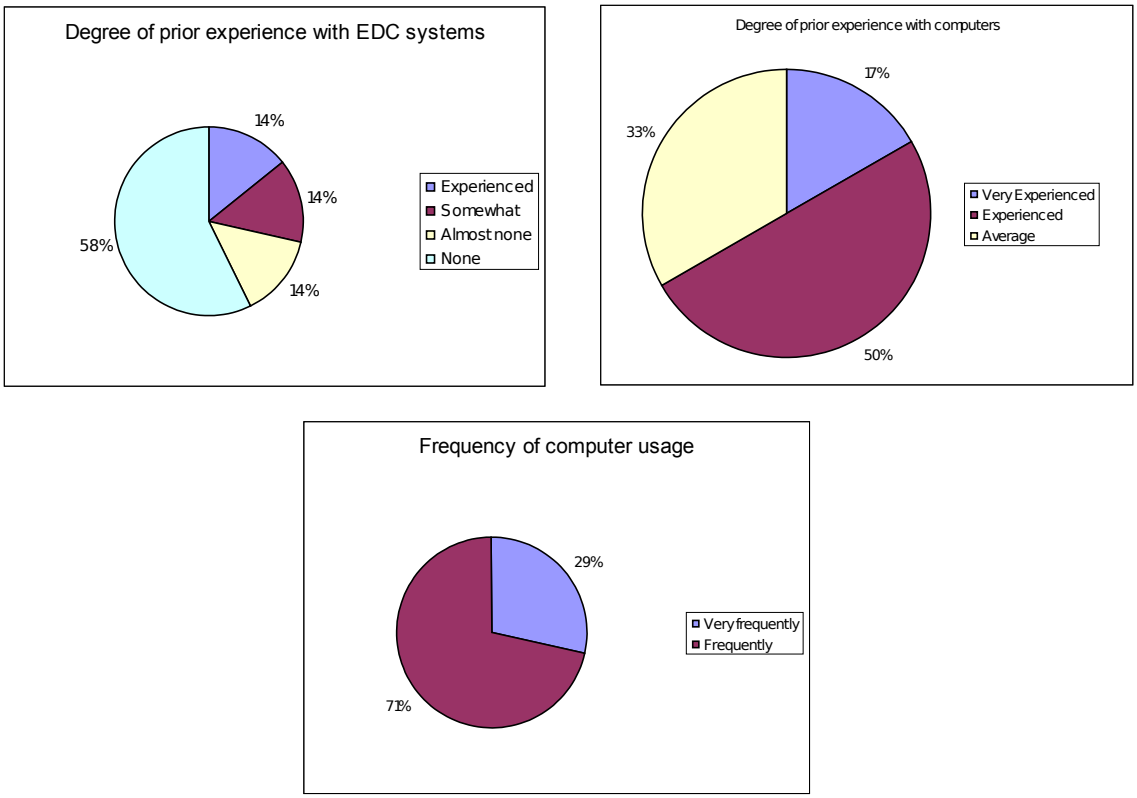


Figure 28: Characterization of users in terms of computer usage and EDC experience

The calculated Cronbach's alpha for each concept evaluated is shown in Table 35.

Table 35: Cronbach's Alpha (reliability of the test)

	Cronbach's Alpha
Usefulness	0.92
Ease of Use	0.76

Factorial validity was assessed by analyzing the twelve questions of the test that are associated with either usefulness or ease of use. Factors vary from -1 (perfectly negative association with the factor) and +1 (perfectly positive association with the factor).

Table 36: Factor analysis results

Question	Factor 1 (Ease of use)	Factor 2 (Usefulness)

Work more quickly	0.46	0.58
Job performance	0.47	0.67
Increase productivity	0.75	0.40
Effectiveness	-0.21	0.82
Makes job easier	0.35	0.80
Useful	0.54	0.78
Easy to learn	0.82	-0.32
Controllable	0.77	-0.24
Clear & understandable	0.80	-0.32
Flexible	0.86	-0.35
Easy to become skillful	0.70	-0.49
Easy to use	0.85	-0.07

Regarding the six "usefulness" questions, the mean rating for the summative results was 37.1 ± 4.3 (maximum of 42). The maximum average results by question were 6.6 ± 0.52 and 6.4 ± 0.91, for items "*I would find the EDC system useful in my job*" and "*Using EDC in my job would increase my productivity*" respectively. The lowest average value was 5.9 ± 1 for the item Job Performance. The average scores are plotted in Figure 29.

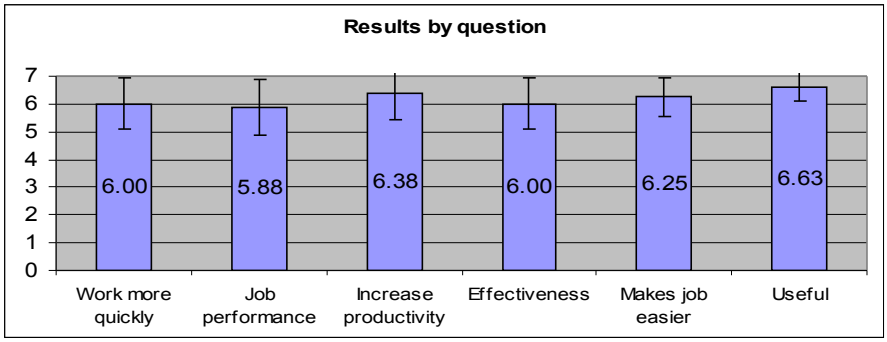


Figure 29: Mean score for "usefulness" answers, by question (bellow) (maximum possible scores was 7 for each question)

The mean rating for the six "ease of use" questions was 36.1 ± 2.9 in a maximum of 42. The maximum average results by question were 6.25 ± 0.46, for items "*Learning to operate the EDC system would be easy for me*" and "*My interaction with the EDC system would be clear and understandable*". The lowest average value was 5.6 ± 0.7 for the item Flexibility.

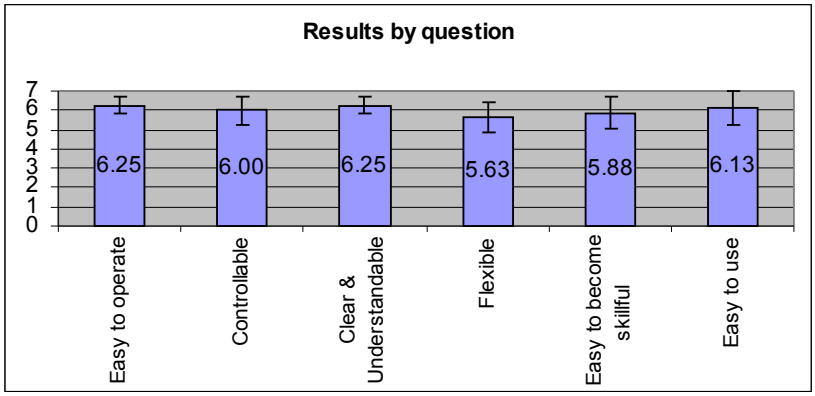


Figure 30: Mean score for "ease of use" answers (maximum possible score = 7)

6.2.2 User satisfaction of the interface questionnaire

Eight users answered the questionnaire. To ensure the reliability of the test with this small sample, the Cronbach's Alpha was calculated. The result of the alpha for the 27 questions of the questionnaire was 0.96. Factor analysis using principal component and rotation results are shown in Table 37, sorted by the factor they were associated with. Four factors were extracted as in J. Chin's questionnaire development study [29] – the four groups of questions of the questionnaire: *terminology*, *learning, screen* and *system capabilities*. Although most items of the *terminology* and *learning* groups are related with its corresponding factors, this association is not clear for the remaining groups similarly to what happens in Chin's article.

Table 37: Factor analysis for the interface satisfaction's questionnaire

Question	Factor 1 (Terminology)	Factor 2 (Learning)	Factor 3 (Screen)	Factor 4 (system capabilities)
Organization of information	0.38	0.51	0.50	0.08
Error messages	0.90	0.16	0.17	0.28
Prompts for input	0.89	0.29	0.21	0.10
System speed	0.88	-0.08	0.10	0.23
System tends to be	0.88	0.35	-0.11	-0.19
Computer informs about its progress	0.87	0.38	0.01	-0.03
System reliability	0.85	0.29	0.32	0.20
Terminology related to task	0.81	0.41	0.29	-0.12
Position of messages on screen	0.80	0.20	0.01	0.19
Supplemental reference materials	0.66	0.39	0.57	0.23
Remembering names and use of commands	0.65	0.38	0.54	-0.20
Reading characters on the screen	0.62	0.02	-0.65	0.38
Exploring new features by trial and error	0.56	0.71	0.36	-0.22
Use of terms throughout system	0.55	0.78	0.22	-0.05
Correcting your mistakes	0.46	0.69	0.48	0.17

Performing tasks is straightforward	0.31	0.94	0.06	-0.03
Learning to operate the system	0.14	0.97	-0.11	0.08
Designed for all levels of users	-0.13	0.44	0.03	-0.77
Help messages on the screen	0.17	-0.40	0.85	0.13
Highlighting simplifies task	0.08	0.33	0.75	0.05
Sequence of screens	0.15	0.35	0.14	0.88

Users rated the system's interface an average of 159.4 ± 16.7. The maximum possible score for the system was 189. Figure 31 shows the average results by question.

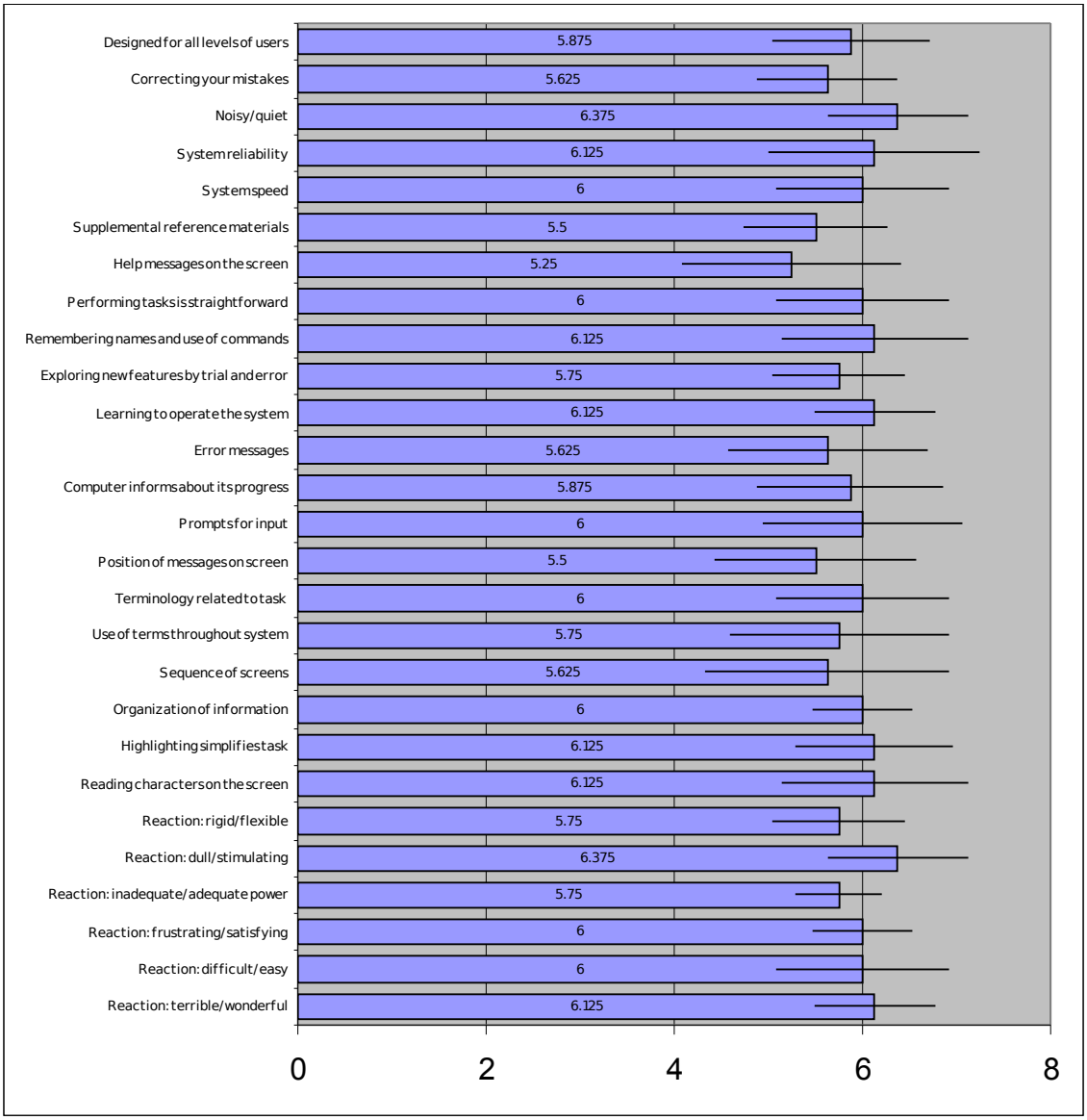


Figure 31: Interface evaluation questionnaire's average results by question (max. score by question = 7)

6.2.3 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 32 shows the distribution of the 20 transcript errors by type.

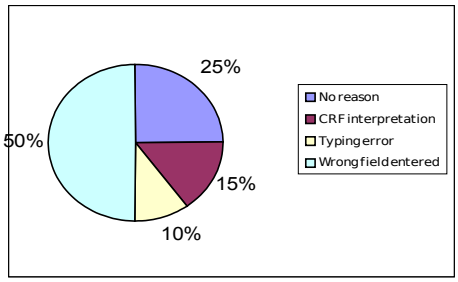


Figure 32: Error type distribution in the transcription phase (total = 20 errors)

In a single data entry process, the error rate would be 5.91 errors per 1000 fields. The double data entry error rate before crosschecking is the sum of the errors made by the two operators, in this case 11.82 errors per 1000 fields (Table 38).

Table 38: Average transcription errors by user, viewed by set of pages transcribed

Pages	Nr fields	Nr errors	Error rate (per 1000 fields)
3,4	336	2	5.95
13-14	678	6.5	9.59
16-17	678	1.5	2.21
Total	1692	10	5.91

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 39).

Table 39: 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. The sample was considered representative of the CRF in terms of data types and data complexity and its size was 69% of the actual CRF. Therefore, the total estimated number of queries was 84. Table 40 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 40: 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

6.3 Pharmacovigilance Database system validation

6.3.1 Test case 1 – Function: Save

Data was inserted in the database according to *Input data 1*. The values in this set data can be found in Annex F.

Data was successfully inserted in the database. However, there was no “close and save button” on the interface. To perform this action, one must click the “Save” button in the form and afterwards close the from by clicking MS Access' drop down functions “File – Close”.

In the laptop where this function was tested it wasn’t possible to slide down to the bottom fields of the form, due to a bug that made the vertical slider disappear. This means that on computers with small *y* resolution the only way to access these fields is by pressing the TAB key on the keyboard.

6.3.2 Test Case 2 - Function: Edit

In this test case an SAR previously inserted in the database was changed according to the data found in *Input data 2* (which can be found in Annex F) . The test was considered successful as the adverse was successfully changed to the new values.

6.3.3 Test Case 3 - Function: Query

The system allows users to query the database by Product, SOC, Seriousness, Predictability, Causality, Font and Notifier. For each query, the user can further filter the results by the SARs' year, product and SAR description (the MedDRA term). The character * can be used as a wildcard in the search, although it cannot be used as a wildcard in the definition of the SARs year.

Each query was tested twice: in the first test the query was filtered with the information for a new SAR inserted according to *Input data 3*. The fields in this input data set should as unique as possible. In the

second test, the query was run with all the wild cards, in order to test if it showed all the AEs in the database.

Table 41 summarizes the test's results. The column *Result* refers to the first sub-test and the column *Result (all entries)* refers to the query run with all the wildcards.

Table 41: Query Function's results

Query by	Result	Result (all entries)
Product	Ok	2)
SOC	Ok	3)
Seriousness	Ok	2)
Predictability	1)	1) 4)
Causality	Ok	5)
Font	Ok	Ok
Notifier	Ok	Ok

Some comments should be made regarding these results:

1. Query parameters are prompted twice. The first parameters are ignored. If second parameters are filled correctly, query result is correct;
2. Must enter SARs' year date for the query to work. Some entries have default year 0 inserted and, therefore, will only show up in the query if begin date is 0. The SARs that have a null value in any of the fields that compose the query did NOT show up in the query result;
3. Same as 2), but query will also fail to show entries without SOC defined;
4. Same as 2), but query will also fail to show entries without predictability defined;
5. Same as 2), but query will also fail to show entries without causality defined

6.3.4 Test Case 4 - Function: Report.

The report function of the software is similar to the query function, the difference being the format the results are displayed. The results are displayed in a printable format, which were exported to PDF files. As in the previous test, the report was first created using data from *Input data 3* as filters and a second report was generated with wildcards as filters. Table 42 shows the results for this test.

Table 42: Report function's results

Query by	Result	Result (all entries)
Product	ok	1)
SOC	ok	2)
Seriousness	ok	2)
Predictability	ok	2)
Causality	ok	2)

As in the previous test case, some issues were detected when in presence of fields with null values:

1. Must enter SARs' year date for the query to work. Some entries have default year 0 inserted and, therefore, will only show up in the query if begin date is 0. The SARs that have a null value in the “year” field did NOT show up in the query result;
2. Same as 1), but also for its parameter.

6.3.5 Test Case 5 – Stress testing of Function: Save

The *Input data 4* test set contained stressful values for the database (check Annex F). The presence of edit checks in the system such as not allowing text characters in the Age or dates fields or having a regex expression for the “Tecnimede AE code” limited the quantity of stress values that could be included.

The SAR was inserted in the database. Some values could not be inserted completely, due to the maximum number of characters for that field. The system's edit checks warned about the problem before saving and didn't let the user save the form with inconsistencies.

6.3.6 Test Case 6 – Backup procedure

Inspection of the backup log of DMED/GT server revealed that the last backup had been completed 5 days earlier, on the date of the last database change.

The backup system performs a full backup once every week and daily incremental backups. A full backup means all files are backed up; the incremental backups only store the files that were changed since the previous backup.

Database is therefore backed up every 24 hours whenever there is a change and/or once every 7 days even when no changes are made to its contents.

6.3.7 Test Case 7 – Access control

The authorization to the system is implemented by the configuration of different levels off access for Windows NT users. There is one user group (Pharmacovigilance R/W) in the department that can access the folder where the database is in with read and write privileges. Other groups don't have any access to the folder.

There are only two NT users that belong to the Pharmacovigilance R/W, belonging to Augusto Filipe (QPPV) and Ana Tomé (Deputy of the QPPV). Unauthorized system user cannot access the folder where the database is stored and therefore cannot change the database.

6.3.8 Test Case 8 – Weighted missing values frequency

73 SARs were randomly chosen and inspected to calculate the weighted missing values frequency. Each SAR had a total of 29 fields, which correspond to a total weight of 46 (recall Table 9).

506 fields were blank in the database, but only a total of 87 fields were classified missing values (recall the criteria for the classification of a missing value). Table 43 shows a list of the missing values (and

errors) found in the database grouped by fields. The greyed fields correspond to information with a weight bigger than one.

Table 43: Missing values and errors found in the database sample (n = 73)

	Missing	Errors	Weight	Weighted missing	Weighted errors
Notifier		19	2	0	38
Patient's Sex		1	3	0	3
Patient's Initials	1		3	3	0
Patient's Age		1	3	0	3
Acknowledgement date	37	2	1	37	2
Batch	6		1	6	0
Concomitant Therapy	2	2	1	2	2
Concomitant Therapy	2		1	2	0
Daily dose		6	1	0	6
Duration	1	3	1	1	3
Evolution		3	1	0	3
Follow up	1	2	1	1	2
Infarmed Code		2	1	0	2
Outcome		1	1	0	1
Predictability	2		1	2	0
SOC	6	3	1	6	3
Therapeutic reason	30		1	30	0
Type of event		2	1	0	2
Worldwide UID		1	1	0	1
Total	87	25			
Total weighted count	90	71			

The total weighted count of the missing values is 90, which yields a missing value frequency of 2,68%.

6.3.9 Test Case 9 – Weighted Error frequency

Table 43 also shows the number of errors count by field in the database sample that was inspected. Although the number of errors is significantly smaller (only 25 errors were recorded) the weighted count is not very different from the previous test: 71. The weighted error frequency calculated is 2,11%.

7 Discussion

7.1 Performance

The average response time of queries in the EDC system was 2.8 ± 2.6 days, while paper queries averaged 49 ± 48 days until they were answered (a 17.5 fold decrease in the average answer time). In addition the complete query process was completed in one week, 27 times shorter than the 191 days in the paper process. The results also show that more than half of the queries were answered in less than one day, demonstrating the dynamism between query issuing and answering when EDC is used.

Although this result can only be valid with the assumptions made previously, EDC definitely proves to be a valuable asset in the reduction of drug development time by providing remote querying of data. Additionally, some queries were answered only hours after having been sent (7 queries were answered in the same day, see Figure 27). In a paper-based process this would be very difficult to achieve (e.g., queries sent through land mail).

Because EDC data was benchmarked against historical data from another study, the comparison between the two times has some limitations. Firstly, the current study's investigators were quicker to respond to queries because they have the conduction of clinical trials as their main job function, while investigators from the previous study were hospital physicians.

The size of the CRFs of the two studies was also considerably different. Differences between CRF sizes can also have influence in the response awareness, i.e. the willingness to respond to a query when it arrives.

In the paper-based process, time from the last clinical trial activity to database lock was 50 days. According to [35], the average time from last subject/last visit to database lock was approximately 36 days, with a range of 20 to 60 days. In the same study, database development had a mean cycle time of 51.5 days. This value is far superior to the 0.5 days considered for a bioavailability database development at the research center (high standardization of bioavailability studies). Another reason worth mentioning is the fact that the database is built in Access, used to build desktop databases and not suited for the development of full web based systems. Therefore, this database is not capable of providing the same features of the EDC system developed (e.g., concurrent remote database access).

Table 44: Performance times benchmarking between paper and EDC processes

	Paper	EDC
Time from last clinical trial activity to database lock	50	37
Time from beginning of process to database lock	89.5	185 ± 16.3

Benchmarking the last clinical trial activity to database lock time reveals a 38% decrease in the EDC case. This value is close to the 43% time save published in [11].

Data review process and especially query management are likely to be the limiting factor in the process of database locking. Given the fact that the paper process produced 2.4 times more queries than EDC, data management should take more time to finish. In addition, the average query response time is estimated to be 17.5 times faster when the EDC system was used, which further contributes to the explanation of why post-trial activities took longer in the paper-based process.

On the other hand, query results show that, of all the trial's post clinical activity days, 73% of the queries were issued in two days, while 88% were answered in two days. This suggests that, prioritizing work in this particular clinical trial at both the sponsor and the research sites could drastically reduce all query activities to two or three days.

Finally, the non-priority state of this clinical trial meant database locking was not completed at the earliest time possible. The database could therefore have been locked considerably sooner than 37 days.

Benchmarking of the total project time, on the other hand, clearly suggests EDC to be a slower process to implement than the paper-based trial. In fact, although all other indicators suggest EDC to be one step in the right direction towards better drug development standards, this project had a 106% time increase when benchmarking against paper – a total of almost three months more. Even if the higher literature value for database development was used, total project development is 150.5 days and EDC process would still be 22.9% slower (34.5 days).

As it was mentioned in the Data management in clinical trials section of the background, a previous study does not recommend as potential candidate studies those with few number of subjects and visits, easy in complexity and small in time (less than 6 months) as good candidates for remote study monitoring [12]. This bioavailability study has all these characteristics.

It should also be noted that a prototype EDC system was developed and, along with providing DMED/ GT with a solution that could be implemented in a pilot study, understanding and defining the main steps in the creation of an EDC system – from database to the interface – were also central objectives of the academic process.

The EDC system was designed for multiple clinical trials. Conversely, the paper-based database is built in Access exclusively for one clinical trial. Later access to the information is more difficult as it is not centralized, and data mining across different clinical trials is almost an impossible mission. EDC system can provide these features and additional interface and database modules can be included in the future..

At the same time, the developers' experience is far greater at this point than in the beginning of the project. It is therefore expected that, as more trials are used with this system, the time required to set up new trials decreases and the system's performance indicators increase in the same proportion.

It is clear that these systems serve different goals. Paper base trials are aimed at solving the issue of data storage and review at an individual level, and are therefore optimized for this objective. For studies of this nature, EDC systems cannot be competitive while this is the main objective in seen at a trial-by-trial level. EDC systems' competitiveness level is raised when it is inserted in a larger data

management solution in clinical research. Data integration among different clinical research activities can be performed in an easier fashion and inter-trial data mining can be conducted. Short term performance gains are expected as trial size rises (in number of subjects, data collected and number of sites) and as the EDC system is standardized.

7.2 Quality

The questionnaires that were conducted show the same degree of reliability and validity than in conditions under which they were developed ([27] and [29]).

In the perceived usefulness and ease of use questionnaire every question was associated with the correct factor in the factor analysis that was performed, except the item “job productivity”- which, contrary to what was expected (see [27]), was associated with ease of use rather than usefulness. The small sample size (N = 8 users) can be on the basis of this difference. Because validity of the test has been previously demonstrated, this item should still be included in the perceived usefulness group.

The overall average rating of 37.1 ± 4.3 is extremely close to the maximum possible result of 42, which shows that users consider the system very useful. The highest valued items were “increase job productivity”, “makes job easier” and “system is useful”. This evidences that, although there is a process change when switching to EDC, the users consider that the change will make them work better and an easier fashion than with a paper process. The lowest ranked item was “job performance”. Even though the average score was very high (5.9± 0.99 on a 1-7 scale), the relative lower score is most likely linked with the process change that needs to be performed when switching to EDC and that requires some adaptation.

The users also find the system very ease to use, as the 36.1 ± 2.9 average summative score indicates. The highest scores were achieved for items “easy to operate” and “clear and understandable”, which is directly related with the interface that was built. This result shows that the effort made to make a practical and user friendly system was successful. The lower result was in the item “flexibility”. This is not a negative aspect per se, as one user noticed when commenting that “Like all eCRFs it has low flexibility, but this can also be seen as a quality”. In fact, when “flexibility” is, as this comment suggests, with “creativity”, the eCRF allows a lower degree of flexibility and enables investigators to make an effort to focus on the essential information that needs to be inserted.

The 159.4 ± 16.7 average summative score for the user satisfaction of the interface questionnaire is 84 ± 8.6% of the maximum possible score (189). This indicates that users’ degree of satisfaction with the system is high.

Factor analysis shows that although most items of the *terminology* and *learning* groups are related with its corresponding factors, this association is not clear for the remaining groups similarly to what happens in Chin’s article. As before, the small sample size can explain this event. Another explanation could be the difficulty in establishing questionnaire validity referred in [29]. Nevertheless, the high degree of reliability of the study (0.96) indicates that questions are measuring the same latent construct (user satisfaction).

Users considered the interface to be stimulating – this was the highest score in the user satisfaction questionnaire. Learning to operate the system was also considered to be easy by users. The training sessions performed to teach users how to operate the system played a decisive role in these results. High scores in the “remembering command names”, “reading characters on screen” and “highlighting simplifies task” items confirms the interface achieved the simplicity that was requested. “Reliability” was also amongst the items with highest score. Even though this was a prototype system, this result shows that users felt the system could be trusted in a clinical trial environment.

Items with lower ratings are mainly related with user help and troubleshooting, such as “help messages on screen”, “position of messages on screen” and “supplemental reference materials”. These results, however, are a paradox when reviewing some of the users’ comments (): the reference materials (SOPs) are described as being “very good”, the problem being that users “read it after the error has occurred”. Another user commented that “feedback from system seems to avoid many mistakes“.

The content and position of messages on the screen are therefore aspects that should be carefully reviewed and enhanced in a future version of the system. One user also added that “error messages sometimes are not very helpful”. Because of the prototype condition of the system, the developing team recognizes this comment to be particularly pertinent. Error messages were hidden and replaced with a “Oops, it seems you have found an error” screen or error labels showed the error in a programming language style. This was a deliberate decision that prevented users from reaching an error page with details about the error written in a programming style of language – incomprehensible to end users. At the same time, error labels with details about the exception launched by the system enabled the development team to quickly discover the origin of the problem and fix it. This aspect was referred by one user, when commenting that “answers were always quick”.

The EDC system developed was able to eliminate transcription errors from the data management process. Using a sample of the CRF of the clinical trial, transcript error rates were calculated to be 5.91 for single data entry and 1.2 for double data entry after crosschecking (per 1000 fields). These values are bellow what was found in the literature [8] and [9] but are nevertheless relevant. The average error rate of 9.59 on pages 13-14 is worth noticing: these pages include data from samples collection, which is directly related with the primary variables of the clinical trial. A 1% error rate in data regarding the main objective of the trial is a risk that is completely eliminated in the EDC process.

The transcription test also proved the utility of double data entry in paper-based processes: the transcription error rate dropped 4.9 times when double data entry was used.

It should also be noted that the CRF of this clinical study was very straightforward. The majority of data was either numerical or multiple choice and there was very little text to be transcribed. Naturally, this fact has influence in both the transcription error rate and the transcription speed, as there is no slowdown or increased errors due to difficulties in understanding handwriting. The degree of difficulty of CRF data has been mentioned as a possible explanation for differences in transcription error rates in another study [9]. A corollary to what has been said is that data types chosen in the sample to calculate transcription error rates are likely to be relevant in the final result.

Differences between operator's degrees of experience can also be on the basis of the discrepancy found between the study conducted and values found in the literature. The degree of experience differences can even be seen between the two operators of the study – operator 1 committed 15 errors versus a total of 5 errors made by operator 2.

The characterization of the type of transcription errors shows that 60% of all errors were human attributable: either typing errors or operators were looking at the wrong field. Although training can minimize this, error is a human characteristic and will always be present in human-dependant processes. EDC processes skip the single/double data entry step, so they will always have this advantage over paper systems that utilize this process.

The total number of queries dropped considerably in the EDC system. The total number of EDC queries was 35, against 84 queries estimated to be issued in the paper CRF. This represents a reduction of 58.4% in the total number of queries. This value is bellow the 86% decrease mentioned in the literature [11] for a 5 country, 19-site trial, but is a remarkable reduction given the fact that it was the first EDC pilot of the company. Questionnaire answers show that 72% of the users are none or almost none experience with EDC systems and, given the fact that this was a prototype system, no user had experience neither with this particular EDC system nor with the new SOPs.

Queries were grouped in six common categories: data consistence, missing data, clarification needed, criteria violation, request additional information and other queries (Figure 33). EDC queries were all grouped in the "clarification needed" and "request additional information" categories, which suggests that the EDC process is not optimized. This optimization should be carried out on three areas: a) learning curve of the investigator and monitor (deeper understanding of the system SOPs) and b) further development of the prototype and SOPs into a final, commercial-ready version).

New clinical trials using a developed version of the EDC system will most likely have decreased values of these two types of queries and increase EDC data quality.

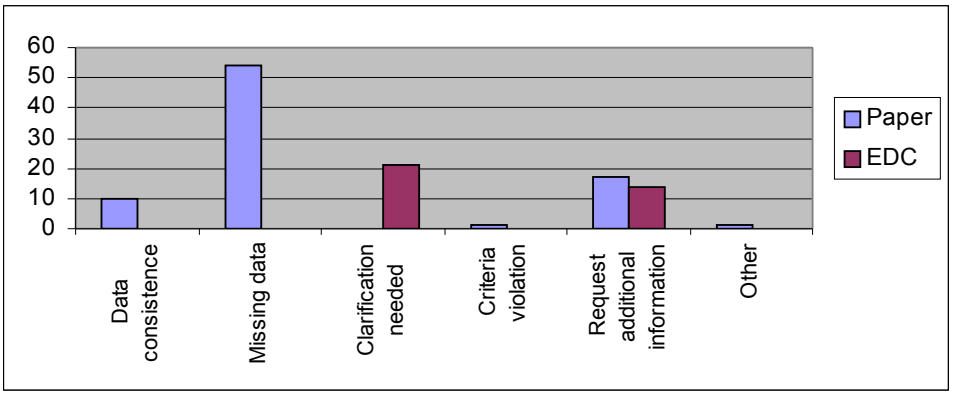


Figure 33: Query grouping in common categories

The same degree of data quality of the current EDC system is achieved more quickly than in the paper version. Immediately after clinical trial activities finish (i.e. before the query process starts), data is already consistent and there is no data missing. Automatic edit checks are likely to be the principal reason behind this improvement. In addition, the EDC system relieves users from cumbersome tasks,

such as signing every page of the CRF or calculating the subjects' body weight or number of adverse events and concomitant therapies recorded.

7.3 Discussion on the validation of the Pharmacovigilance Database

7.3.1 Save and edit functions

The save and edit tests were successful. According with the acceptance criteria, the tests should be considered successful if the SAR are in the database and if the information is identical to the input data.

The system's form for the introduction/edition of SARs does have some issues regarding horizontal and vertical scrolling. While vertical scrolling is not an issue in its daily use due to the sufficient vertical resolution of the computer monitors of the terminals that use the system, switching to another application while having the SAR form opened would cut around 60% of the save/undo buttons.

After enquiring the system's users, it was discovered that the error might have been introduced after a system change. Due to the current software life cycle phase of the product – and because this is a legacy system – it is recommended that the system is not further altered (which would imply a new validation). Instead, the users should adopt the following guidelines:

1. Do not use the system on a computer with a monitor with a vertical resolution of 800 px or less.
2. Do not switch to another application while inserting or editing an Adverse Event in the database.

The stress values' test of the database (*Test case 5*) also revealed that the system is capable of dealing with these values satisfactorily. The edit checks in place make it impossible for a user to insert wrong values on some fields, as stated in the previous section. This functionality enhances the robustness of the system, enables the elimination of some errors caused by user distraction and prevents the database from throwing errors if data types are not compatible (recall the discussion in the Events and navigation section).

In the case of very long strings of text that exceed the maximum number of characters for a database field, the system warns the user that the input string is bigger than the maximum allowed, not allowing the user to save the impossible value. This functionality is in concordance with the acceptance criteria of the test case: the SAR is inserted in the database and *if insertion is rejected due to impossible values or wrong data, the tester should correct the impossible/wrong format values and try to insert the AE again.*

One remark should be made regarding the *Patient's Age* field. Even though the implementation of this field as an integer seems reasonable, a standard procedure should be in place for the event of a patient with less than one year of age. Lack of such procedure will result, as noticed in the retrospective validation of fields, in the registration of a patient with an age of "0", which is incorrect

and does not distinguish this patient from the patients whose age was not available. It is therefore recommended that users adopt the guideline:

- If the patient is less than one year old, it should be recorded as having 1 year of age

7.3.2 Query and reporting functions

Both the query and reporting functions' tests were successful in returning the SAR inserted according with the information in *Input data set 3*, for every type of criteria in the "*query/report by"* field. There was, however, an issue with the "query by predictability" function, which repeated the query parameters and disregarded the first set of parameters inserted. If the parameters are correctly specified the second time, however, the result is correctly displayed. It can therefore be safely assumed that, even though the *query by predictability* function has a unsatisfactory UI, the results are not affected if users are trained to adapt to this interface. Therefore, and once again justified by the life cycle phase the software is in, it is recommended that the following guidelines are adopted:

- Do not change the queries
- Users are instructed to skip the first set of parameters in the *query by predictability* function.

When querying and reporting all the SARs in the database (using wildcards as query parameters), some SARs were not shown in the result. This happened whenever an SAR had a null value for at least one of the fields that composed the query. For example, the product query can filter SARs by year, product and SAR description (MedDRA description). Because one of the SARs in the database didn't have any SAR description defined, it wasn't shown in either the query result nor the query report.

This issue is caused by a combination of three factors:

a) bad query design

The SQL equivalent to what is probably coded in the query is the string

WHERE *attribute1* = $1 AND *attribute2* = $2 AND....

attributeX is each query parameter (product, description, year, etc.) and *$X* is the corresponding string input inserted by the user. The problem with this query is that whenever *attributeX* is null, the comparison is false and therefore the result is not appended. The correct SQL should be:

WHERE (*attribute1* = $1 OR *attribute1* IS NULL) AND (*attribute2* = $2 OR *attribute2* IS NULL) AND ...

b) insufficient edit checks in form

Another way to prevent the issue from existing would be to ensure the user cannot leave any fields blank when saving the AE.

c) insufficient training

A last, operational level solution to the problem would be to train users not to leave any fields blank when operating with the database. The last solution is simultaneously the less robust and the easiest to implement.

Again due to the life cycle phase of the software, and due to the reduced number of users of the system, it is recommended that the last solution is applied as soon as possible. It should be noticed, however, that this is only a remedial action that does not prevent the defect but only reduces its probability.

The tests were therefore only partially successful. If the tests were to be conducted on a software currently in development, it would be mandatory that the errors were corrected before the system was deployed in a production environment.

7.3.3 Backup procedure and authorization control

The requirements for the Pharmacovigilance Database specify that the database should be backed up at least once every week. The result for the backup test case indicates that the system is in compliance with this requirement, as the database is backed up weekly in the worst case scenario (when no change is made) and within 24 hours whenever a user changes its contents. This backup is considered to be sufficient for the level of usage the database (and the risk associated with it). The test was therefore considered successful.

The system requirements 3 and 9 concerned authentication and authorization to access and use the system (recall Table 24). The main concern is that unauthorized users should not have access to the system and only users with sufficient privileges should have edition privileges (insert, edit or delete adverse events).

Although MS Access does not permit this degree of control, authorization and authentication was implemented using network wide control access in DMED/GT. A Windows NT user group was created and configured to be the only group to have access to the directory the database is in and only two users belong to that login group. The authentication is done when the user logs in to the workstation. Although this poses a possible security threat if the user logs in and leaves the workstation unattended, it is a common solution as an authentication mechanism. Moreover, the security risk is highly minimized by adequate training of personnel, which again stresses the importance of users' qualification when operating with computerized systems, as it is vastly referenced in the literature ([17, [36],[19,[18]). The access control test was therefore also considered successful.

7.3.4 Weighted missing values and error frequencies

According to the requirements, the maximum error frequency allowed for the system is 5%, while the maximum allowed missing value frequency is 2%. These values already take into consideration the different weights the fields should have according to their relative importance.

The missing values' frequency was determined to be 2,68%, which is above the threshold value defined in the requirements. A more thorough analysis was therefore made to investigate the reasons behind this requirement failure. A careful look at Table 17 reveals a very high frequency of missing values on the therapeutic reasons and acknowledgment date fields. In fact, out of the 73 SARs analyzed, 41% (therapeutic reasons) and 50,6% (acknowledgment date) had a missing value for these fields. Upon speaking with the QPPV and his deputy, it was discovered that these two fields had only

been introduced in the database in December of 2007, along with another field named *literature article*. A retrospective correction of the old SARs was not performed, although new SARs entered after that date contained the information for the new fields. This information is corroborated by the missing values' analysis data: in the 9 newest SARs in the database sample analysed, there was only one missing value for the acknowledgment *date* field and no missing values were found for the *therapeutic reasons* field.

In the light of this new information, the missing values' frequency was re-calculated removing the missing values from these fields. There was a significant difference in the missing values' frequency, dropping from 2,68% to 0,68%, which is considerably bellow the validation threshold.

Due to the fact that the previous calculated missing values' frequency didn't take into consideration the information about the late introduction of the two fields in the database, the new frequency of 0,68% was accepted and the test was therefore considered successful.

The existence of this problem – and the fact that it was only discovered upon speaking with the QPPV after performing the validation activities – does, however, underline two important findings of the validation activity:

1. Validation should cover operation and maintenance

An FDA finding revealed 79% of its software recalls were originated by errors made after a change was made to the original software. The validation activity performed in the pharmacovigilance system proved this finding to be true: even though there was no error introduced in the software, a change made to the original system and a lack of operational strategy to retrospectively correct the data originated a high increase in the missing values' frequency.

2. All changes should be clearly documented

The validation process' usefulness is very little if there is no documentation to prove it. Similarly, software documentation, from a user manual to a system description and list of requirements and a record of all the changes made to the system after its initial version are of key importance to confirm it is performing according to what is expected. In this system, the lack of documentation regarding changes made to the number of fields regarding an Adverse Event made it impossible for the head of the validation process to know that some fields were not available in the database for most of the software's life.

Had this information been available, an exclusion to the validation activities could have been defined to disregard any missing values or errors found in these fields for adverse events inserted before a specific date.

With regard to the weighted error frequency, the value of 2,11% is bellow the maximum error frequency of 5% defined in the requirements, and therefore the test was considered successful.

A closer look at the origin of the errors, however, also reveals that the majority of the errors were recorded in the *Notifier* field. This contribution was further amplified by the weight of this field (2), due to the fact that the notifier is one of the minimum pieces of information necessary to record an adverse event (according to EMEA). The vast majority of these errors were due to the fact that the user

recorded “Doctor” as the notifier, even though the “Healthcare Professional” box was checked. Although recorded as an error, it should be noted, however, that a doctor is a healthcare professional and therefore the user only interpreted the source document and probably read the job title of the AE submitter. This error, however, can lead to two interesting conclusions:

1. System design and documentation has impact on the quality and validity of data

In this case, the possible choices for the *Notifier* are Consumer, Doctor, Healthcare Professional, Nurse, Pharmacist or Unknown. It is clear that doctors, nurses and pharmacists are all healthcare professionals, so the existence of these options alongside the possibility to choose “Healthcare Pprofessional” can lead to confusion.

Possible solutions that would avoid this problem could be the definition of only one of the choices (either only have *Healthcare Professional* or the specific job titles) or, in alternative, having a clear procedure in the documentation that defines how users should make their decisions in case of doubt.

2. Training is essential

The corollary to the previous conclusion is that adequate training of users is essential for the success of an electronic data capture system. Even if the system is well designed and documentation is available, the system may not work as expected if the users are not trained to operate with it.

7.3.5 Validation summary

Table 45 summarizes the results of the test plan activities.

Table 45: 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

In the light of these results, the software was considered successfully validated with restrictions. The problems found in the system are not considered to be severe and do not affect its performance significantly, as long as users are made aware of these issues and are trained to overcome them, as it was suggested in the previous sections.

Because the Pharmacovigilance Database is a legacy system, a system review and correction will imply a new validation process that is not justified given the expected end-of-life time for this system.

The system complies with all requirements (listed in Table 24). However, for requirements 6 and 7 (ability to query the system and produce reports) to be met the users must be trained to use the system. In particular, users must be trained not to leave any field blank when inserting an SAR in the database and SARs already in the database should be reviewed to ensure no entry has null values for the fields *AE year,seriousness, notifier, predictability, causality and AE description.*

The validity of the software should therefore only take place after the following actions are performed:

1. A user's manual containing the guidelines suggested in the previous sections is written and available to users;
2. Users are trained to follow these guidelines and a written evidence of this training is available.

It is highly recommended that the company prepares a plan to phaseout the Pharmacovigilance Database and replaces it with a more robust system that can better integrate with the pharmacovigilance business process. A new system specifically designed to meet the requirements and challenges of the gold standards in pharmacovigilance management can improve business performance and, at the same time, contribute as a module of a wider CTMS. A new system could be designed as more than a repository of information, and could be integrated with other systems such as the eCRF developed.

7.3.6 Validation maintenance

Once the validated state has been achieved, a set of rules must be established to maintain this state.

7.3.6.1 Security level

A list of the login groups with read and write privileges to the database should be available at all times, as well as a list of users that belong to those login groups. This list should be updated whenever changes occur and should be reviewed every six months.

7.3.6.2 Operational level

Users must be trained before using the system. A record of the training sessions should be maintained alongside the rest of the documentation. All the documentation regarding the system and its validation should be archived in secure conditions and be readily available to users or regulating authorities. The training should cover the operational procedure to perform the system's functions, and should have a special focus on the guidelines referred previously that cover operations that can compromise the quality of the data.

7.3.6.3 Changes

It is highly recommended that the current system is not changed and that its phaseout is prepared. However, if small changes are to be made to the system, Table 46 indicates the activities that are to

be performed to maintain the system's validated state. All changes should be registered and added to the system's documentation.

Table 46: Strategies in case of change

Change	Activities
Change in form layout	The functions that access the form should be re-validated according to the Test Cases in the Test Plan.
Change in field (type, number of characters, edit checks)	All functions (save, edit, query, report) should be re-validated according with the Test Plan
Addition of a field to the database	Documentation should define how backward compatibility with the AEs already entered in the database is done

7.3.6.4 Periodic Review

To ensure the validated state of the software, periodic review should be performed on the system. Inspectors are advised to check for the procedure that ensures on-going evaluation of the system and what change control procedures are in place [19].

System review should take into consideration the risk associated with the system. For the Pharmacovigilance Database, it is advisable that the system is reviewed every two years, if no changes have been made to the system. The revision should encompass the re-running of the tests in the Test Plan.

According to the literature, the review tests can be based on an abbreviated version of the original tests whenever that is possible [36]. For the system tested, the missing values and error frequencies could be calculated using the values found for the previous validation test and adding a random selection of new adverse events to maintain the the confidence level and margin of error (recall the expression in Figure 25).

8 Future work

The innovative character of this work at the national level leads to the conclusion that there is room for improvement in this area. Future work in the EDC system can be viewed from a bottom-up perspective, from operational improvements to architecture and business decisions and ideas.

At the operational level, focus should be given to error handling. Future versions of the system should refrain from showing technical errors to end users. One path that can be taken is the development of an automatic error reporting tool that sends error details automatically to the developers and provides further support to users.

Edit checks can also be further developed. Current edit checks only warn users of data invalidity when the eCRF page is opened. eCRF milestones (discussed bellow) could enable edit checks warnings to be automatically sent to clinical trial monitors after certain dates or events occur. In addition, an interesting feature that could be developed is the automatic suggestion of inclusion or exclusion criteria answer, whenever possible (e.g. if diastolic pressure is bellow the minimum required in the protocol, the system should suggest the subject's exclusion). The final decision should, as always, be left to the investigator.

Current audit trail support in the interface is limited to its exportation to an xml Excel/Openoffice document. Future research should be conducted to define and implement an audit trail visualization tool in the web interface, as well as enhance its exportation capabilities.

At a higher, conceptual level, the entire system should be reviewed to improve its ability to receive multiple trials. One of the recommended improvements is the review of clinical trial activities to transform them into events. Each event is composed of different tasks (questions or exams) and each period is composed exclusively of various events. This idea is further explained in [25]. At the interface design level, this development should lead to the increase in its modularity. One of the main factors that increased total development time was the high number of web components (pages) that needed to be created – one for each exam. Modularity is aimed at reducing the number of interface pages built by grouping them in categories.

The importance of the validation process when developing software in a highly regulated environment was shown. Further development of the eCRF system should take these findings into consideration and validation activities should be planned in parallel with the system's development.

The reintroduction of data in the validation process created the opportunity to compare entries in the original and cloned database sample. This comparison can enable the determination of the robustness of the pharmacovigilance process currently active. In particular, the comparison between fields that are prone to human interpretation, such as the SARs' *seriousness*, *predictability* and *causality* can determine how much the information contained in the system is dependent from the user that inserts it. A high dependence on the user can indicate a deficiency in the business process that can even affect its validity or interest.

Both at the interface and database levels, the system review should also include the concept of clinical trial milestones. On larger clinical trials, this could be a valuable asset to give feedback to the project manager on clinical trial activities and warn them of possible delays (e.g.: number of enrolled subjects is less than expected, milestone is that enrollment should be completed in date x). The achievement of milestones could trigger actions such as automatic edit checks that ensure every task belonging to a certain period has been performed.

Multiple trial capabilities are particularly important to improve system flexibility and setup time. The primary variables of these trials are related to drug concentrations in the human body, which means the clinical phase is usually composed of a number of periods where biological samples are collected from the volunteers. Although figures such as the exact number of samples collected or the number of subjects enrolled can vary, the trials possess a high degree of similarity. Just as in the paper based process, where this factor was referred as one of the main reasons for the reduced time for setting the database up, EDC systems must be built in such a way that subsequent trials are set up and run in a quick and easy fashion.

Continuing a bottom-up approach, at the architecture decision level an area of future research is the development of new interface mediums. In particular, the adaptation of this EDC system to PDAs would be interesting. The development of an interface for PDAs is independent of the system ‘s database layer. Another interesting interface is a touch screen laptop.

The concept behind these alternative interfaces is relieving investigators from the keyboard so that EDC becomes easier in a hospital scenario. The interfaces are therefore meant to complement and not replace the current interface, as the monitors’ work is probably easier using a web interface with a common screen resolution.

Finally, at a business level, the understanding of a common ground between different Electronic Data Capture systems, such as the eCRF and a Pharmacovigilance Database opens the ground to the creation of a CTMS. This modularity can enable a phased development of different parts of the system and independent validation of them. It should be noted however, that the integration of independent systems or different modules must be viewed as equally important to the validation process. A cost analysis of the EDC prototype will definitely be a step in the right direction regarding validation of this process. Having showed that data quality is improved by EDC, time performance must travel in the same direction to make the cost-benefit ratio favorable to EDC adoption. Cost metrics should be defined for clinical trial activities (including pre and post clinical trial) so that a precise cost benchmark of EDC vs. paper is performed.

9 Conclusion

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. This project was the first of its kind to be conducted at the academic level in Portugal. In addition, no information about similar projects developed at the industry level in Portugal is published. Information about EDC in Europe is scarce compared with the United States.

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. This option enables EDC systems to improve its performance (provided the application server is designed to meet the expected usage levels) – and make performance independent of the client. Centralized process logic also improves maintainability, reusability in different clinical trials, as well as it eases scalability, while it makes the system available anywhere with an Internet connection.

Performance benchmarks show 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 in the entire process. 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 therefore 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.

Taking in consideration the international regulations regarding the validation of computerized systems in the pharmaceutical industry, 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 SARs' information in electronic format. The SARs are associated with drugs tested in clinical trials or already launched to the market. The system was developed in Microsoft Access and has been in use since the early 2000's.

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 (IT, users) 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 to test if the requirements were met. It consisted 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's save and edit functions were tested successfully, both for normal and stressful values, while the query and reporting functions were only partially successful. The reason behind the partial failure of these two tests was insufficient training of users, combined with the inexistence of edit checks to prevent null values from existing and/or queries that took into consideration their existence.

The backup procedures and access control tests were also successful. The weighted error frequency and weighted missing values' frequency were calculated to be 2,11% and 0,68% respectively, which are both bellow the requirements (5% and 2%).

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. Further features can be created at a latter stage as separate modules of the system.

Further development of the EDC system should take into consideration the importance of the validation activities and focus on improving system error feedback and edit checks at the operational interface level. At the architecture level, the database and interface should be revised to improve system modularity that can reduce setup time in the pre-clinical phase of the projects. Alternative interfaces such as PDAs and tablet PCs should be considered to improve the system’s flexibility and portability. Lastly, a cost analysis of the improved EDC system can provide additional information about the advantages of EDC in the industry.

Annexes

Annex A - Use cases' description

- **Access validation**

    a) eCRF validation

        1. When accessing the website, users are presented with a login screen;
        2. The user shall insert his credentials, which correspond to his electronic signature (alphanumeric username and password);
        3. The system verifies the data entered;
        4. After successful login the user is shown the initial page, specific for his user role.

    b) Database validation

        1. Only the system administrator shall have access to the database through the DBMS;
        2. Login is composed of a username and a password;
        3. The DBMS validates the login and access is granted to the clinical trial database.

- **Add subjects to the trial**

Previous steps required: access validation

1. A list of the enrolled subjects shall be available after selecting a clinical trial;
2. The option “Add New Subject” enables the user to perform this action. The subject will be added after basic demographic information is recorded and the informed consent date is specified;
3. After the subject is added a work area will be created and access to its eCRF granted.

- **Automatic Edit Checks (performed by the system)**

Previous steps required: user inserts data in fields with edit checks enabled

1. Inserted or altered data is subject to the programmed edit check. If the inserted data is rejected by the edit check, output information shall warn the user;
2. If the user wishes not to change the data, the system shall let the incorrect data to be inserted. A visual indication of a potential error (such as a red box around the value) shall be present to inform users of the situation.

- **Data entry and data changes in the eCRF**

Previous steps required: access validation; eCRF and/or clinical trial is not locked

1. Anonymous users cannot enter or alter data;

2. Investigators can enter/alter eCRF data (periods, CT and AE);
3. Monitors can change eCRF data and, together with the investigator, close the eCRF;
4. Data managers can enter/alter data from eCRF, except database administrative tools, and can lock or unlock the clinical trial database;
5. Project managers can enter or change the trial's administrative data;
6. System administrators can enter/change any non-clinical trial related data;
7. Data is subject to edit checks;
8. Every data change is recorded in the audit trail.

- **View eCRF data**

Previous steps required: access validation

1. System administrators can view all data regarding the clinical trial he/she administers;
2. Investigators can view eCRF data (periods, CT and AE), trial's randomization and queries sent to his/her investigating center;
3. Monitors and data managers can view eCRF data (periods, CT and AE) and all clinical trial queries;
4. Project managers can view the same information as monitors and also clinical trial administrative data.

- **Subject exclusion**

Previous steps required: access validation;

1. Subject's exclusion can occur at any moment after he has been enrolled;
2. Exclusion is performed by accessing the "Subject study completion" area and filling out the reasons for study abandon;
3. The subject's status shall change to "excluded from clinical trial".

- **eCRF (un)Lock**

Previous steps required: access validation; all eCRF data has been inserted;

6. The investigator and monitor can close an eCRF by electronically sign and date the "CRF Closeout" page (re-entering his login credentials);
7. The eCRF is considered closed only when both an investigator and a monitor sign them;
8. To unlock the eCRF the user must access the trial administration tools and select the eCRF to unlock from the list.

- **Query issuing**

Previous steps required: access validation;

1. Each eCRF page is linked with a query issuing tool which enables users to write and send a query;
2. After a query is sent, a warning system shall inform the principal investigator of the new query. A copy of the query shall be sent to the user who issued the query.

- **Query answer**

Previous steps required: access validation;

1. An interface shall list all the queries the user has access to and which queries remain unanswered;
2. Each query shall have a link that sends the user to the specific page where the query was sent from;
3. The user may need to enter/change data. Afterwards, the query must be answered and sent;
3. Similarly with query issuing, a warning system shall inform the user who issued the query of its answer. A copy of the answer shall be sent to the user who answered the query.

- **Trial data export (including audit trail export)**

Previous steps required: access validation;

1. User with project management privileges can export clinical trial data. An interface shall allow the user to select data to export – all data or sub-sets of data from specific trial periods, specific investigating centers or specific subjects;
2. Data shall be exported in an appropriate format, such as XML, and be available for download after the user has requested it.

- **Drug concentration data management**

Previous steps required: access validation; relevant period data inserted;

1. After the user receives data from the laboratory in the Excel format, he shall be able to enter it in the database by means of an interface;
2. When uploading data, and before it is inserted in the database, a control system shall be in place to confirm that there were no errors in the upload process and that the excel template is correct. This system shall, for example prompt the user to insert randomly selected concentration values.

- **Clinical trial data lock**

Previous steps required: access validation; all clinical trial information has been inserted;

1. A specific location in the clinical trial's details section shall have an option to lock the clinical trial;

2. After confirming the lock by inserting the user's credentials, the database is locked and information is stored regarding lock date. No further data change can occur.

- **Clinical trial unlock**

Previous steps required: access validation; all clinical trial information has been inserted;

1. A specific location in the clinical trial's details section shall have an option to unlock the clinical trial;
2. After confirming trial's unlock by inserting the user's credentials, the database is unlocked and information is stored regarding the unlock date. The trial's data is available for change again.

- **Insert source documents**

Previous steps required: access validation;

1. Source documents must be inserted in the eCRF. Required source documents are laboratory results, ECGs, medication labels and any source documents regarding an adverse event;
2. The interface shall allow users to insert source documents and relate them with the corresponding subject and period.

- **Create user accounts**

Previous steps required: access validation;

1. User accounts are created directly on the database, by inserting the user's first and last names, email, phone number, username, password, user role and user center.

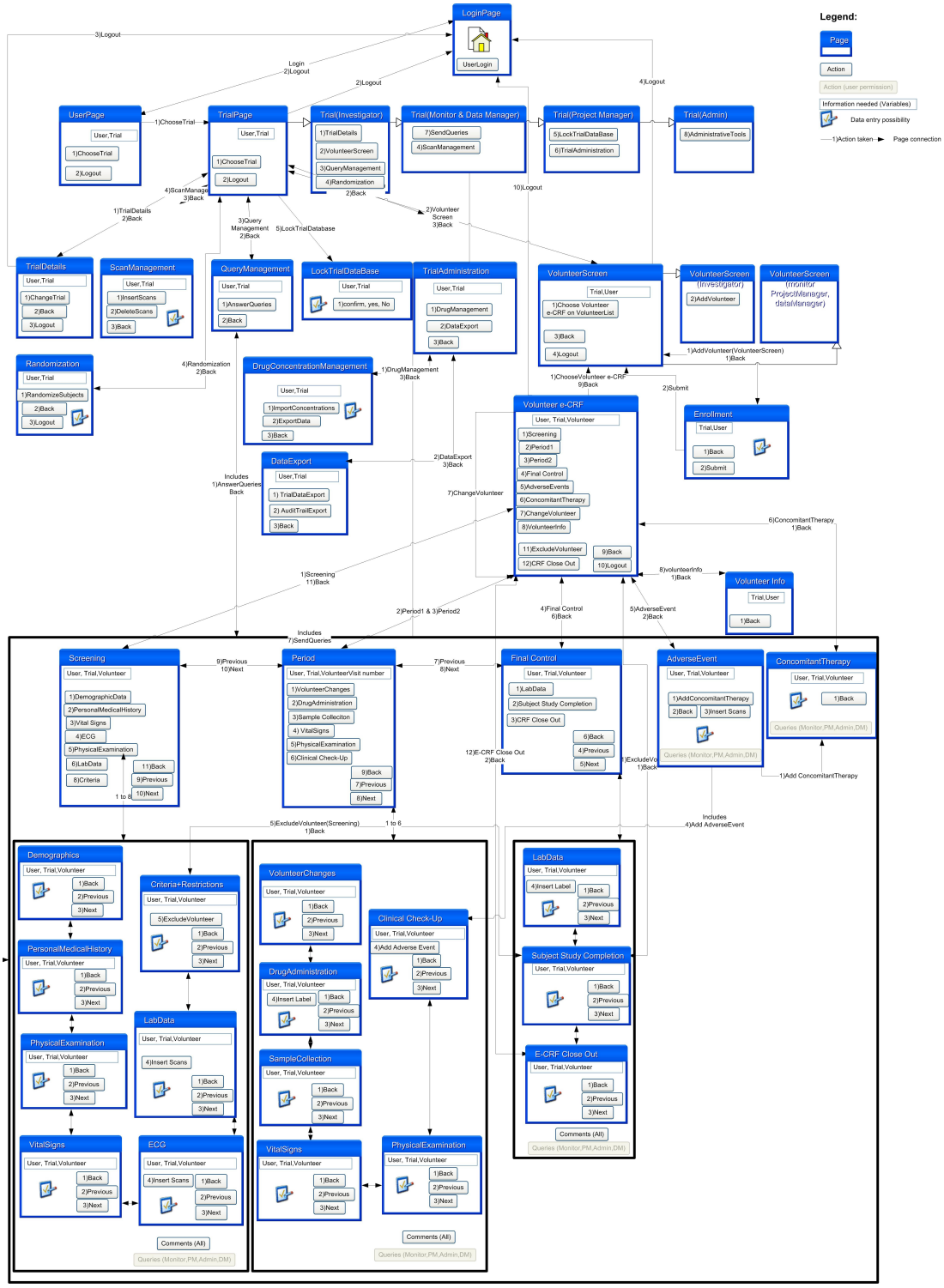
- **Database administration**

Previous steps required: access validation;

Database administration includes:

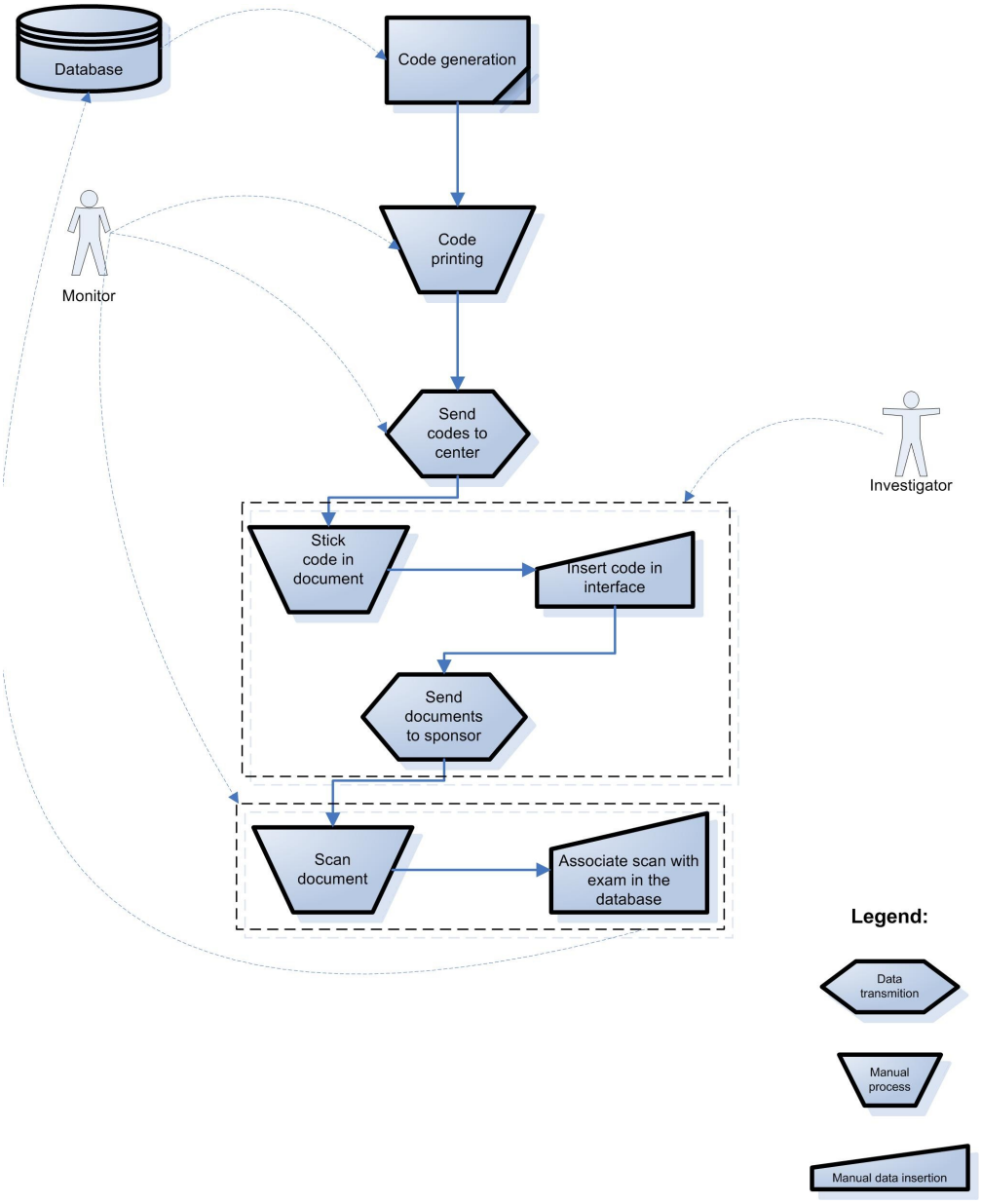
1. Insert data directly in the database;
2. Alter data directly in the database;
3. View data directly in the database.

Annex B – Interface design



Each object represents one interface component – in this case, a web page – and the connections available in each component (the boxes in each component). The lines represent the state changes that occur when a specific option is selected. The  icon represents data entry possibility by users.

Annex C - Process diagram for source documents' handling



Annex D - Pharmacovigilance database fields and their stress values

Field	Data type	Choice type	Constraints	Stress values
Código GTM	Text	Open text	1234/56/AB	Very long string
Código INFARMED	Text	Open text	1 letter and 9 numbers	Very long string
Worldwide Unique case ID	Text	Open text	17 characters	Very long string
Iniciais Doente	Text	Open text	9 characters	Integer, long string
Idade	Integer	Open text	Less than 1000000	Text, negative number
Sexo	Character	Multiple Choice	M/F	NA
Data (dia)	Integer	Multiple Choice	01-31	NA
Data (mês)	Integer	Multiple Choice	0-12	NA
Data (ano)	Integer	Multiple Choice	1994-2028	NA
Duração (minutos)	Integer	Open text	Less than 999	Text, negative number
Duração (hora)	Integer	Open text	Less than 999	Text, negative number
Duração (dias)	Integer	Open text	Less than 999	Text, negative number
Código(s) MedDRA	Text	Open text		Text, negative number,long string
Termo(s) MedDRA (Descrição)	Text	Open text		Very long string
SOC	Text	Multiple Choice	Choice from List	Very long string
Tipo	Text	Multiple Choice	2 values	NA
Gravidade	Text	Multiple Choice	3 values	NA
Intensidade	Text	Multiple Choice	4 values	NA
Fonte	Text	Multiple Choice	4 values	NA
Previsibilidade	Text	Multiple Choice	3 values	NA
Notificador	Text	Multiple Choice	6 values	NA
Follow-up	Text	Multiple Choice	4 values	NA
Nexo de causalidade	Text	Multiple Choice	6 values	NA
Evolução	Text	Multiple Choice	8 values	NA
Produto	Text	Open text		Very long string
Lote	Text	Open text		Text?
Dose diária	Text	Open text		Negative values, long string
Indicação terapêutica	Text	Open text		Very long string
Trat. Concomitante	Text	Open text		Very long string
Observações	Text	Open text		Very long string
Artigo de literatura	Text	Open text		Very long string
Data de conhecimento	Text	Open text		Wrong format

Annex E - Validation Test Plan

1.Summary

This document defines the protocol for all tests that will be conducted under the scope of the validation plan of the Pharmacovigilance Database version DI/2.00.

Each test considered on the validation plan will be detailed in this document, including all data inputs that were utilized and the outputs it produced.

1. Test Case 1 - Function: Save

1.1.Test Objective

Assess the Save function of the software with normal values. This function allows a user to register a new AE in the database.

1.2.Test requirements

Requirement type	Description	Documents/data
Input data	Information of the AE which will be inserted on the database	Input data 1

1.3.Test Procedure

Step	Screen	Action
1.	None	Open the database
2.	Main Menu	Choose “Insert new AE”
3.	AE Form	Insert data as defined in “Input data 1”
4.	AE Form	Click save button
5.	Main Menu	Query database by inserted AE's code

1.4.Acceptance criteria

Adverse Event is inserted in the database. Last step should yield a screen with the new AE. Test is passed if and only if the information is identical to the input data.

2.Test Case 2 - Function: Edit

2.1.Test Objective

Assess the Edit function of the software. This function allows a user to change information of an existing AE in the database.

2.2.Test requirements

Requirement type	Description	Documents/data
Input data	Information of the changes to the AE	Input data 2
Previous information	At least one AE should be inserted on the database.	

2.3.Test Procedure

Step	Screen	Action
1.	None	Open the database
2.	Main Menu	Choose “View AE” and choose one AE
3.	AE Form	Change AE's data according to “Input data 2”
4.	AE Form	Click save button
5.	Main Menu	Query database by inserted AE's code

2.4.Acceptance criteria

Adverse Event is changed in the database. Last step should yield a screen with the AE. Test is passed if and only if the information is identical to the input data.

3.Test Case 3 - Function: Query

3.1.Test Objective

Evaluate the query functions of the software. This function allows a user to query the database and retrieve listings of the entries, filtered and ordered by various fields.

3.2.Test requirements

Requirement type	Description	Documents/data
Previous test	Test case 1 and 2 should be conducted before this test	Test case 1 Test case 2
Input data	Input AE information	Input data 1
Input data	Input AE information	Input data 2
Input data	Input AE information. Information should be distinct from Input data 1 + Input data 2.	Input data 3

3.3.Test Procedure

Step	Screen	Action
1.	None	Open the database
2.	Main menu	Insert a new AE, according to Test Case 1, and using input data 3.
3.	Main Menu	Choose “query by product”
4.	AE Form	Leave all filters blank, except the filter “product name”. Write the product name according to Input data 1 + Input data 2.
5.	Query result	Determine if result is expected according to the acceptance criteria
6.	Query result	Go back to main menu
7.	Main menu	Repeat the test with the next query option.
8.	Main menu	Repeat steps 1-7. On step 4, leave all filters blank

3.4.Acceptance criteria

Each query should produce a list of items of a size N + 1, where N is the number of events on the database before test case 1 that pass the query filter and 1 corresponds to the AE inserted in test case 1. Because Input data 3 should be distinct, this adverse event should not be shown on any of the lists, except the queries produced in step 8. The result of the queries produced in step 8 should be a list of items of size N + 2.

4.Test Case 4 - Function: Report

4.1.Test Objective

Evaluate the report functions of the software. This function allows a user to query the database and print a report of the listings produced, filtered and ordered by various fields.

4.2.Test requirements

Requirement type	Description	Documents/data
Previous test	Test case 1 and 2 should be conducted before this test	Test case 1 Test case 2
Input data	Input AE information	Input data 1
Input data	Input AE information	Input data 2
Input data	Input AE information. Information should be distinct from Input data 1 + Input data 2.	Input data 3

4.3.Test Procedure

Step	Screen	Action
1.	None	Open the database
2.	Main menu	If it hasn't already been done, insert a new AE, according to Test Case 1, and using input data 3.
3.	Main Menu	Choose “report by product”
4.	AE Form	Leave all filters blank, except the filter “product name”. Write the product name according to Input data 1 + Input data 2.
5.	Report result	Export result to available format
6.	Report result	Go back to main menu
7.	Main menu	Repeat the test with the next report option.
8.	Main menu	Repeat steps 1-7. On step 4, leave all filters blank

4.4.Acceptance criteria

Each query should produce an exportable report of size N + 1, where N is the number of events on the database before test case 1 that pass the query filter and 1 corresponds to the AE inserted in test case 1. Because Input data 3 should be distinct, this adverse event should not be shown on any of the reports, except the reports produced in step 8.

The reports produced in step 8 should have a size of N + 2. Exportable reports should be confirmed either by printing or by the production of a PDF.

5.Test Case 5 – Stress testing of Function: Save

5.1.Test Objective

Assess the Save function of the software with stress conditions. Stress conditions are defined in the validation plan.

5.2.Test requirements

Requirement type	Description	Documents/data
Input data	Input data with stress conditions	Input data 4

5.3.Test Procedure

Step	Screen	Action
1.	None	Open the database
2.	Main Menu	Choose “Insert new AE”
3.	AE Form	Insert data as defined in “Input data 4”
4.	AE Form	Click save button
5.	Main Menu	Query database by inserted AE's code

5.4.Acceptance criteria

Adverse Event is inserted in the database.

If insertion is rejected due to impossible values or wrong data, the tester should correct the impossible/ wrong format values and try to insert the AE again.

Last step should yield a screen with the new AE. Test is passed if and only if the information is identical to the input data.

6.Test Case 6 – Backup procedure

6.1.Test Objective

Assess the backup procedure is in accordance with software specification.

6.2.Test requirements

Requirement type	Description	Documents/data

6.3.Test Procedure

Step	Screen	Action
1.	None	Determine de date of the current backup of the database
2.	None	Determine the periodicity of the backup procedure

6.4.Acceptance criteria

Last backup should be one week old or newer. Backup procedure should be configured to back up the database at least once every week.

7.Test Case 7 – Access control

7.1.Test Objective

Assess the access control policy implemented and ensure only authorized users have edit privileges in the database.

7.2.Test requirements

Requirement type	Description	Documents/data
Input data	Input AE information	Input data 1
Previous information	At least one AE should be inserted on the database.	

7.3.Test Procedure

Step	Screen	Action
1.	None	Access the database through an unauthorized terminal
2.	Main menu	Insert an AE, according with the procedure in Test Case 1 and using Input data 1
3.	Main menu	Open an already inserted AE
4.	AE Form	Change the value in the field “Observações” to: “Test Case 6 – Access control” and save.

7.4.Acceptance criteria

Test is passed if and only if:

1. The AE in step 2 is not successfully inserted on the database
2. The field “Observações” is not successfully changed in step 4.

8.Test Case 8 – Weighted missing values frequency

8.1.Test Objective

To determine the weighted missing values frequency of the fields in the database.

8.2.Test requirements

Requirement type	Description	Documents/data
Retrospective data values	The database currently in use, with AE already inserted	
Source data	Source documents in paper	Source documents
Documentation	Requirements documentation, with the definition of what constitutes an error on the database and how weighted error frequency is calculated	Software Requirements Documentation
List of AE	Random list of source AE documents, of pre-determined size	List of Adverse Events
Operator	Steps 6 to 9 will have to be conducted by an experienced user in the system	

8.3.Test Procedure

Step	Screen	Action
1.	None	Access the database
2.	Main menu	Open the first AE on the database
3.	AE Form	Compare the information on the database with the corresponding source document(s). Register the number of missing values
4.	AE Form	Go back to the main menu and repeat the procedure with the next AE
5.	AE Form	Exit the database
6.	None	Open a new, empty database
7.	Main menu	Select “new AE”
8.	AE Form	Insert first AE of the AE List
9.	Main Menu	Repeat steps 7-8 for every AE on the list
10.	Main Menu	For every AE on the database created in step 6, repeat steps 2-4, comparing only the fields: MedDRA code, MedDRA term(s), SOC
11.	None	Calculate the weighted missing values frequency and compare it with the error frequency defined in the Requirements Documentation

8.4.Acceptance criteria

Test is passed if and only if weighted missing values frequency is less than what defined in the Requirements documentation.

9. Test Case 9 – Weighted Error frequency

9.1.Test Objective

To determine the weighted error frequency of the fields in the database.

9.2.Test requirements

Requirement type	Description	Documents/data
Retrospective data	Data already on the database	
Source data	Source documents in paper	Source documents
Documentation	Requirements documentation, with the definition of what constitutes an error on the database and how weighted error frequency is calculated	Software Requirements Documentation
Independent consultation	Whenever doubt arises as to assess equality between source documents and database fields, two independent, experienced professionals shall be consulted.	

9.3.Test Procedure

Step	Screen	Action
1.	None	Access the database
2.	Main menu	Open the first AE on the database
3.	AE Form	Compare the information on the database with the corresponding source document(s). Register the errors.
4.	AE Form	Go back to the main menu and repeat the procedure with the next AE
5.	None	Calculate the weighted error frequency and compare it with the error frequency defined in the Requirements Documentation

9.4.Acceptance criteria

Test is passed if and only if weighted error frequency is less than what defined in the Requirements documentation.

Annex F - Input data sets

Field	Input data 1	Input data 2	Input data 3	Input data 4
Código GTM	0123/45/AA	9876/54/ZZ	0000/99/XX	012345678901234567890-ABCDEFGHIJ
Código INFARMED	C1234567890	987654321	9876	012345678901234567890-ABCDEFGHIJ
Worldwide Unique case ID	PT/-AA//1999/XX	EN.ty-33.9	WW-Case./xx	012345678901234567890-ABCDEFGHIJ
Iniciais Doente	ITC	MR	MR2	ABCDEFGHIJ01234
Idade	33	99	98	-24
Sexo	M	F	M	M
Data (dia)	31	1	2	29
Data (mês)	12	1	1	2
Data (ano)	1994	2008	2008	2004
Duração (minutos)	62	0	12	-1
Duração (hora)	25	1	12	-1
Duração (dias)	32	0	12	-1
Código(s) MedDRA	99999999	111222900	1112229	-12345678901234600000
Termo(s) MedDRA (Descrição)	Some MedDra term	Some other term	Some third MedDRA term	The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog
SOC	Blood and Lymphatic System Disorders	Cardiac Disorders	Eye Disorders	SOC term a
Tipo	ACONTECIMENTO ADVERSO	REACÇÃO ADVERSA	ACONTECIMENTO ADVERSO	ACONTECIMENTO ADVERSO
Gravidade	GRAVE	NÃO GRAVE	GRAVE	GRAVE
Intensidade	N	L	M	M
Fonte	ESTUDO CLÍNICO	AUTORIDADE REGULAMENTAR	ESPONTÂNEA	ESPONTÂNEA
Previsibilidade	ESPERADO	NÃO ESPERADO	NÃO SE APLICA	NÃO SE APLICA
Notificador	MÉDICO	CONSUMIDOR	ENFERMEIRO	ENFERMEIRO
Follow-up	TERMINADO	EM DECURSO	NÃO INDICA	NÃO INDICA
Nexo de	CERTO	PROVÁVEL	CONDICIONAL/NÃ	CONDICIONAL/NÃO CLASSIFICADO

causalidade			O CLASSIFICADO	
Evolução	CURA	Não recuperado	Desconhecido	Desconhecido
Produto	Ácido Alendrónico Farmoz	Produto foo	Produto xx	Produto abcdefghijklpmnopqrstuvwxyz_012345678 90
Lote	TM99XX12		1	22-JJ
Dose diária	120 mg/dia	1 microg/dia	3 comprimidos/dia	-11 comprimidos revestidos por dia, ou -2 comprimidos por dia sem sintomatologia
Indicação terapêutica	Indicação terapêutica x	Indicação terapêutica y	Indicação terapêutica z	The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog
Trat. Concomitante	Medicamento A – x mg/dia; Medicamento B – y inalações/dia		Medicamento Y	The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog
Observações	Observação complementar 1	Observação complementar 1; Nova observação	Sem observações	The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog
Artigo de literatura	Autor P, Autor S, Título do Artigo, Publicação, 1999	Autor P, Autor S, Título do Artigo, Publicação, 1999	Título X	The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog, The quick brown fox jumps over the lazy dog
Data de conhecimento	12-12-00	01-01-02	03-03-07	ABR-23-2007

Annex G – Perceived usefulness and ease of use questionnaire

Percieved Usefunlness and Ease of Use questionnaire

Try to respond to all the items.
For items that are not applicable, use: NA
Add a comment about an item by clicking on its
To send your results, click on: Finish and send Questionnaire.
To save your questionnaire without sending it, click on: Save.

question	answer	comment
User experience *Degree of prior experience with computers*	None ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very Experienced	
User experience *Degree of prior experience with EDC systems*	None ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very Experienced	
User experience *Frequency of computer usage*	None ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very Experienced	
Percieved Usefullness *Using ClinIT-EDC in my job would enable me to accomplish tasks more quickly*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Percieved Usefullness *Using ClinIT-EDC would improve my job performance*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Percieved Usefullness *Using ClinIT-EDC in my job would increase my productity*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Percieved Usefullness *Using ClinIT-EDC would enhance my effectiveness on the job*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Percieved Usefullness *Using ClinIT-EDC would make it easier to do my job*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Percieved Usefullness *I would find ClinIT-EDC useful in my job*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Perceived Ease of Use *Learning to operate ClinIT-EDC would be easy for me*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Perceived Ease of Use *I would find it easy to get ClinIT-EDC to do what I want it to do*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Perceived Ease of Use *My interaction with ClinIT-EDC would be clear and understandable*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Perceived Ease of Use *I would find ClinIT-EDC to be flexible to interact with.*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	
Perceived Ease of Use *It would be easy for me to become skillful*	Unlikely ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Likely	

Annex H – User satisfaction of the human-computer interface questionnaire

Questionnaire for User Interface Satisfaction

question	answer	comment
Overall Reaction to the Software *terrible/wonderful*	Terrible ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Wonderful	
Overall Reaction to the Software *difficult/easy*	Difficult ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
Overall Reaction to the Software *frustrating/satisfying*	Frustrating ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Satisfying	
Overall Reaction to the Software *inadequate power/adequate power*	Inadequate power ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Adequate power	
Overall Reaction to the Software *dull/stimulating*	Dull ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Stimulating	
Overall Reaction to the Software *rigid/flexible*	Rigid ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Flexible	
Screen *Reading characters on the screen*	Hard ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
Screen *Highlighting simplifies task*	Not at all ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very much	
Screen *Organization of information*	Confusing ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very clear	
Screen *Sequence of screens*	Confusing ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very clear	
Terminology and System Information *Use of terms throughout system*	Inconsistent ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Consistent	
Terminology and System Information *Terminology related to task*	Never ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Always	
Terminology and System Information *Position of messages on screen*	Inconsistent ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Consistent	
Terminology and System Information *Prompts for input*	Confusing ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very clear	
Terminology and System Information *Computer informs about its progress*	Never ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Always	
Terminology and System Information *Error messages*	Unhelpful ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Helpful	
Learning *Learning to operate the system*	Difficult ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
Learning *Exploring new features by trial and error*	Difficult ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
Learning *Remembering names and use of commands*	Difficult ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
Learning		

Learning *Performing tasks is straightforward*	Never ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Always	
Learning *Help messages on the screen*	Unhelpful ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Helpful	
Learning *Supplemental reference materials*	Confusing ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Very clear	
System Capabilities *System speed*	Too slow ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Fast enough	
System Capabilities *System reliability*	Unreliable ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Reliable	
System Capabilities *System tends to be*	Noisy ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Quiet	
System Capabilities *Correcting your mistakes*	Difficult ○1 ○2 ○3 ○4 ○5 ○6 ○7 ◉NA Easy	
System Capabilities *Designed for all levels of users*	Never ○1 ○2 ○3 ○4 ○5 ○6 ◉7 ○NA Always	

	List the systems' aspect(s):
Negative aspect	
Negative aspect	
Negative aspect	
Positive aspect	
Positive aspect	
Positive aspect	

References

[1] Spilker B. Guide to Clinical trials. 1st Edition. NY: Raven Press; 1991. p. 74.

[2] ICH. Guideline E9 - Statistical Principles for Clinical Trials. EU: EMEA; 1998.

[3] Green J A, The EDC Value Proposition to the Pharmaceutical Industry Part II, DataTrak International Inc, p29, September 2001.

[4] ICH. Guideline E3 - Structure and content of clinical reports. EU: EMEA; 1996.

[5] ICH. Guideline E6 - Good clinical practice. EU: EMEA; 1996.

[6] Hoseken J. EDC - turning the corner? [Document on the Internet]. PharmaFocus feature; October 2003 [cited 2006 December 1]. Available from: http://www.pharmafocus.com/cda/focusH/1,2109,22-0-0-OCT_2003-focus_feature_list-0-0,00.html

[7] Jacobson A. The emergence and adoption of electronic data capture (EDC) in clinical trials data collection. edc Today [technical bulletin]. 2002; 1:4 pages Available from: http://www.edcmanagement.com/

[8] Reynolds-Haertle RA, McBride R. Single vs. double data entry in CAST. Control Clin Trials [abstract]. 1992; 13(6):487-94.

[9] Johnson G. A comparison of accuracy, speed, and task satisfaction between paper-based and image-based data entry of case report forms. MSc [Research report]. Liverpool: Liverpool John Moores University; 2000.

[10] Clinical Data Interchange Standards Consortium - Electronic Source Data Interchange (eSDI) Group. Leveraging the CDISC Standards to Facilitate the use of Electronic Source Data within Clinical Trials [version 0.5]. CDISC; 2005.

[11] Peachey J. The eClinical equation, Part 1: Electronic Data Capture. IBM Business Consulting Services; 2005.

[12] Bart T. Comparison of electronic data capture with paper data collection. London: Touch Briefings; 2003.

[13] Spink C. Pharmaceutical Clinical Development - Electronic Data Capture (EDC) as a means for e-clinical trial success. IBM Global Services – LifeSciences; 2002.

[14] Green J A, The EDC Value Proposition to the Pharmaceutical Industry Part II, DataTrak International Inc, p29, September 2001.

[15] Department of Health and Human Services. 21 CRF Part 11. FDA. USA; 1997.

[16] Department of Health and Human Services . Guidance for Industry Part 11, Electronic Records; Electronic Signatures – scope and application. FDA. USA; 2003.

References

[17] Department of Health and Human Services. Guidance for Industry: Computerized systems used in clinical trials. FDA. USA; 1999.

[18] Department of Health and Human Services. General principles of Software Validation; Final Guidance for Industry and FDA staff. FDA. USA; 2002.

[19]PIC/S. Good Practices for computerized systems in regulated "GXP" environments. PIC/S. 2007.

[20] Hanover J, Julien E. US Clinical trial management systems 2004 vendor analysis: Leadership grid and market shares [Document on the Internet]. IDC Life Sciences Insights; 2004 [cited 2006 December 1]. Available from: www.oracle.com/industries/life_sciences/IDC_CTMS.pdf

[21]Mestler J et al. EDC 101 - A high level view of a very broad subject. IIR – EDC and Beyond Conference; Las Vegas: 5-6 April 2006.

[22]Jacobson A. EDC's Impact on Clinical Data Management: Metrics, Best Practices, and Decision Making. edc Today [technical bulletin]. 2002; 6:6 pages Available from: www.edcmanagement.com

[23] Pfleeger S. Software Engineering Theory and practice. 2nd Edition. New Jersey: Prentice Hall; 2001. p.135-94.

[24] Netcraft. November 2006 Web Server Survey [Document on the Internet]. Netcraft News; 2006 [cited 2006 December 1]. Available from: http://news.netcraft.com/archives/2006/11/01/november_2006_web_server_survey.html

[25] Santos M. Design of a Database System for Electronic Data Capture in Clinical Trials. 5 year degree [Final Project Report]. Lisbon: Instituto Superior Técnico; December 2006.

[26] AMB/01/03/II/P/(R). Ensaio Clínico multicêntrico com distribuição aleatória, aberto e paralelo, para avaliar o efeito do ambroxol cápsulas a 120 mg em doses crescentes na concentração de óxido nítrico no ar expirado, em doentes com asma brônquica persistente, ligeira ou moderada. Departamento Médico, Grupo Tecnimede.

[27] Davis F. Perceived Usefulness, Perceived Ease of use, and user acceptance of information technology. MIS Quarterly. 1989; 13(3): 318-41.

[28] Taylor A. A brief introduction to factor analysis [Document on the Internet]. Macquire University Online – Department of Psychology. Australia. 2001. Available from: http://online.mq.edu.au/pub/PSYSTAT/other/FactorAnalysis.PDF

[29] Chin JP, Diehl VA. Norman KL. Development of an Instrument Measuring User Satisfaction of the Human-Computer Interface. In: Soloway, Elliot, Frye, Douglas, Sheppard, Sylvia B, editors. Proceedings of the ACM CHI 88 Human Factors in Computing Systems Conference; 1988 June 15-19; Washington DC, USA. p. 213-218.

References

[30] Siconolfi RM, Bishop S. RAMP (Risk Assessment and Management Process): An Approach to Risk-Based Computer System Validation and Part 11 Compliance. Drug Information Journal. 2007; 41: 69–79

[31] Lander V. 21 CRF Part 11 and Risk Assessment: Adapting fundamental methodologies to a current rule. Pharmaceutical Technology. 2004. May

[32] Microsoft Corporation. Microsoft Access 2002 System requirements. Available from http://office.microsoft.com/en-us/access/HA102132351033.aspx

[33] ICH. Guideline E2 - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. EU: EMEA; 1995.

[34] RD McDowall. Effective and Practical Risk Management Options for Computerised System validation. Quality Assurance Journal. 2005; 9:3

[35] Fitzmartin R. A survey of industry best practice metrics in clinical data management and biostatistics. Drug Information Journal. 2001; 35: 671-79

[36] ACDM/PSI Working Party. Computerized systems validation in clinical research – A practical guide. Macclesfield, Chechire.1998.