

Audit a studi con CRF elettronica

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Riunione sottogruppo GCP- GIQAR

Agenda

- **Regulatory Context**
- **eCRF and process**
- **Audit Focus**
- **Main Findings**

Audit a Studi Clinici con eCRF

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Background

- Audits verify the compliance with the GCP, the clinical study protocol and the applicable regulatory requirements
- Use of eCRF should ensure the GCP compliance (paper CRF = eCRF)
- To ensure audit efficacy, the auditor should have the necessary know how concerning the requirements for electronic data management.

Regulatory Context (1/3)

- Declaration of Helsinki, October 2008
- ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

Regulatory Context (2/3)

- Title 21 Code of Federal Regulations (21 CFR Part 11) - Electronic Records; Electronic Signatures - March, 2000
- FDA -Computerized System used in Clinical Investigations, May 2007
- GAMP (Good Automated Manufacturing Practice)
- INS-GCP-3 Annex III to Procedure for conducting GCP inspection requested by the EMEA- Computerised Systems
<http://www.emea.europa.eu/Inspections/GCPproc.html>

Regulatory Context (3/3)

Data Protection

- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Decreto Legislativo 30 giugno 2003, n.196 - Codice in materia di protezione dei dati personali, vigenza 27 febbraio 2004
- Deliberazione n.52 del 24 luglio 2008 - Linee guida per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali

GCP and Data Integrity

The Note for Guidance on Good Clinical Practice:

Sets out many of the basic principles that are needed for the implementation of electronic documentation, although they are mainly described in the context of data collection and transformation.

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provide assurance that **the data and reported results are credible and accurate** and that the rights, integrity and confidentiality of trial subjects are protected.

GCP Requirements for records and reports

GCP 4.9 (Records and reports)

4.9.1 The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained

4.9.3 Any change or correction to a CRF should be dated, initialed and explained...Sponsors should provide guidance to Investigators on making such corrections. Sponsor should have written procedures to assure that changes or corrections in CRFs made by Sponsor are documented, are necessary and are endorsed by the Investigator

GCP requirements for Electronic Data Management

GCP 5.5.3 (Trial Management, Data Handling, and Record Keeping)

- When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:
 - a. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. **validation**).
 - b. Maintains **SOPs** for using these systems.
 - c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an **audit trail**, data trail, edit trail).
 - d. Maintain a list of the **individuals** who are **authorised** to make data change
 - e. Maintain adequate **backup** of the data
 - f. Safeguard the **blinding**, if any (e.g. maintain the blinding during data entry and processing).

GCP requirements for TMF

TMF

8.2.2 CRF

To document Investigator and Sponsor agreement to the CRF

8.3.2 Any revision to CRF

To document any revisions

8.3.14 Signed, dated and completed CRF

To document that the Investigator confirms the observations recorded

8.3.15 CRF Corrections

To document all changes/additions or corrections made to CRF after initial were recorded

Requirements for data quality

Security

Integrity

Traceability

Data shall be
(regardless
the format !)

Attributable

Legible

Contemporaneous (timeliness)

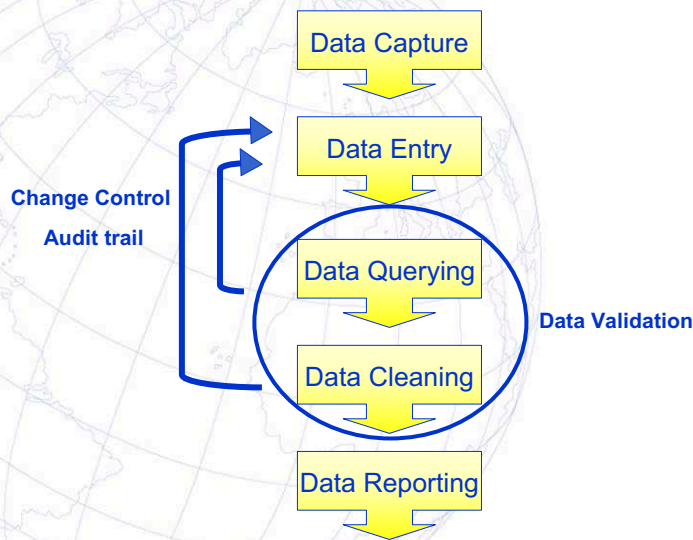
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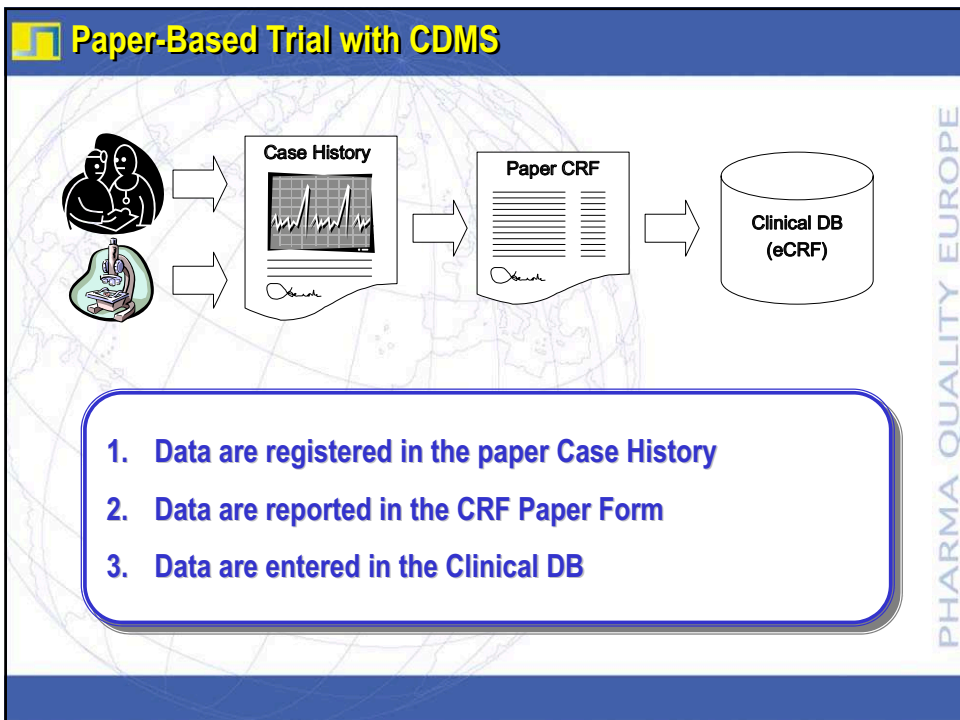
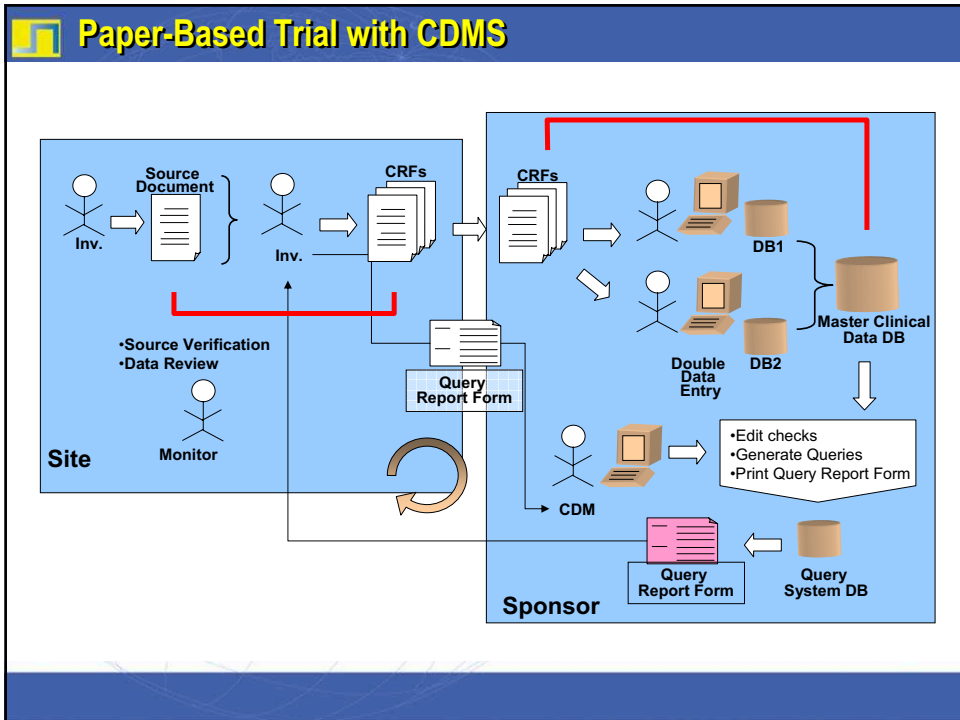
Accurate

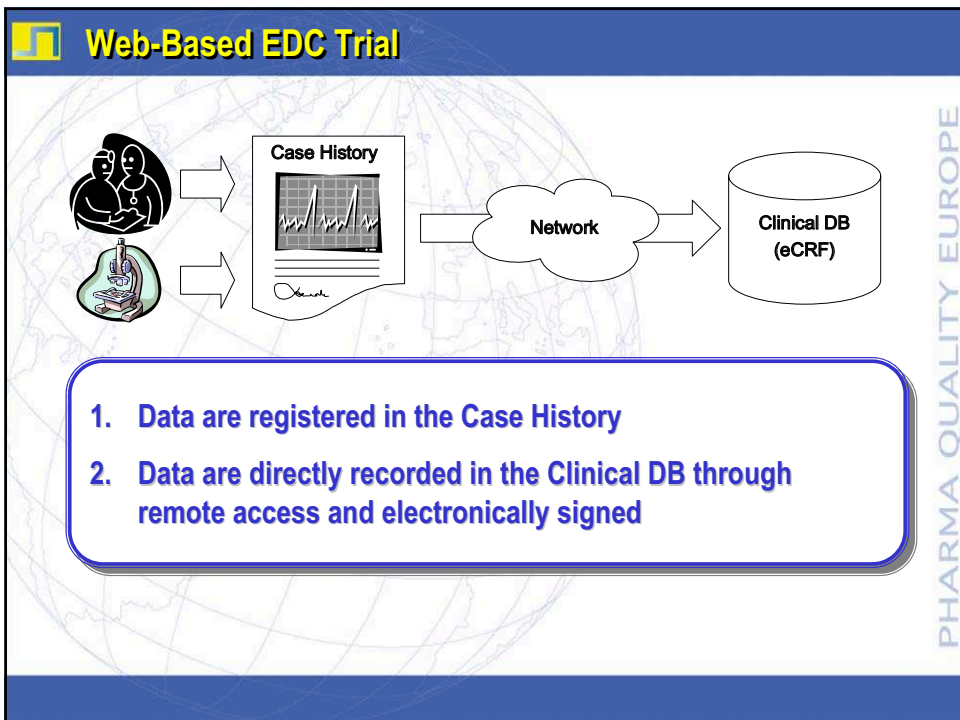
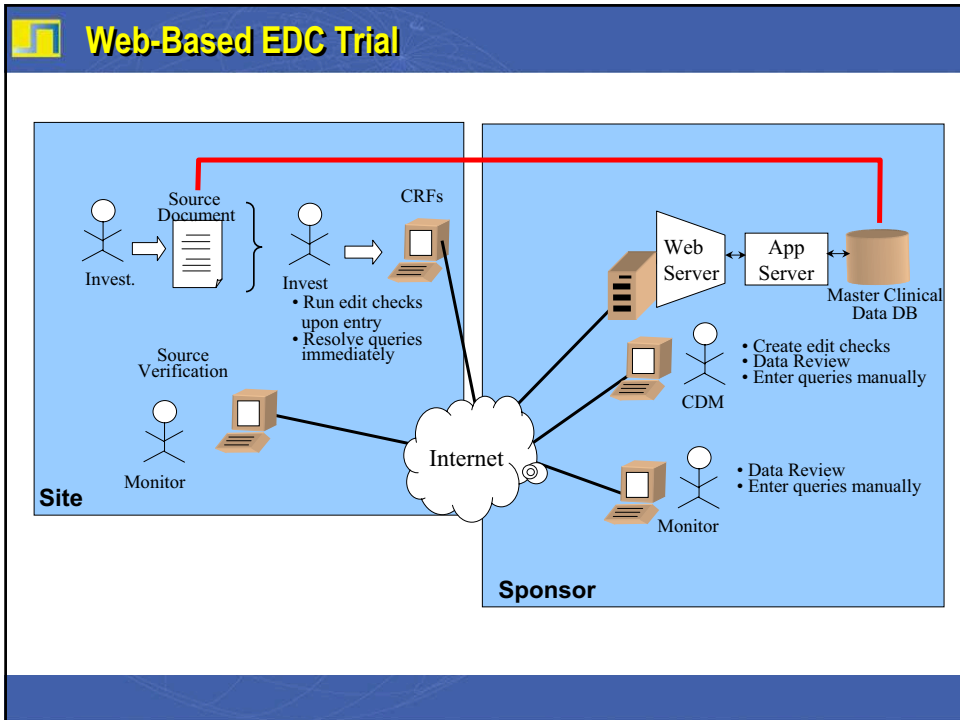
Audit a Studi Clinici con eCRF

- Regulatory Context
- eCRF and Process**
- Audit Focus
- Main Findings

eCRF System - Main process





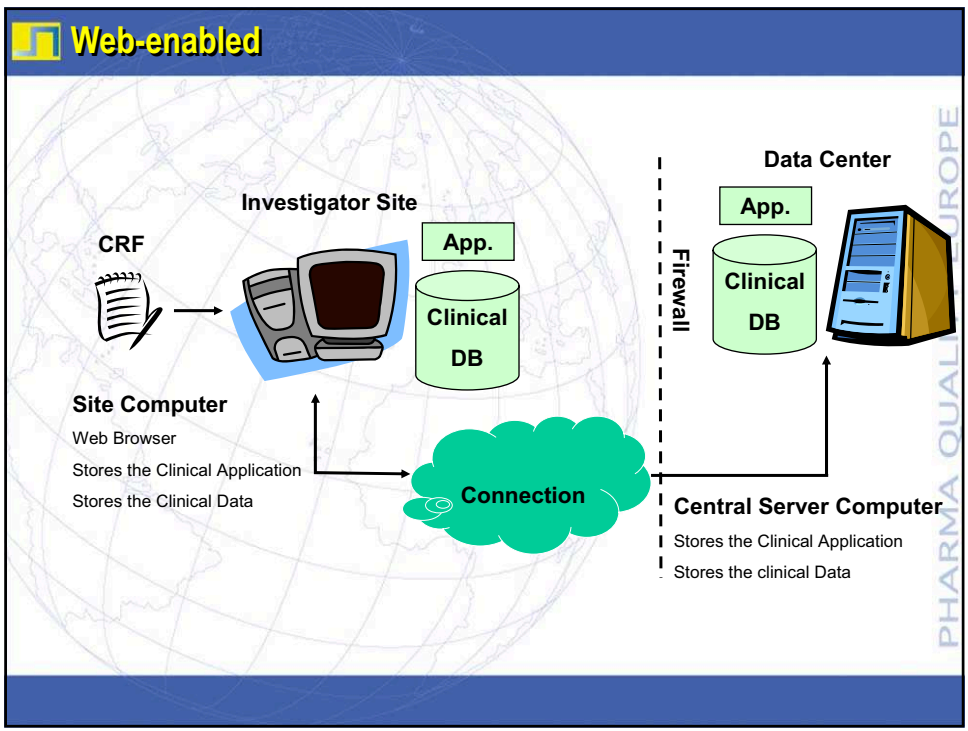
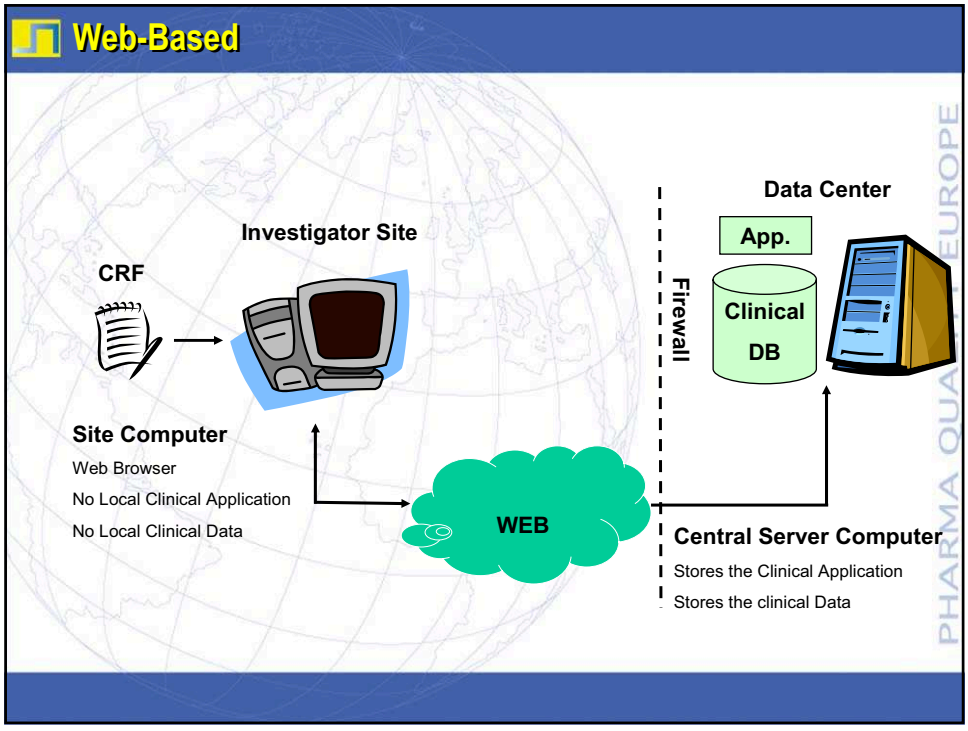


E-CRF and the process

- Data are entered into CRF and database by investigator (single data entry)
- Source data are verified by Monitors, after having been entered into database
- Data are subject to data quality checks by the Data Manager of the Sponsor
- Discrepancy resolution is done by the Investigators

e-CRF: Different End User Configurations

- Web-based
- Web enable



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PHARMA QUALITY EUROPE

eCRF Audit approach

At Sponsor site

On TMF

At site

At Investigator site

At site

PHARMA QUALITY EUROPE

eCRF Audit approach

At Sponsor		At Site
✓	CSV process	Informed
✓	Testing	
✓	Release	✓
✓	Maintenance	Informed/Trained
✓	Training	✓
✓	Security	✓
✓	Data Entry	✓
	Usability	✓
✓	TMF Archiving	✓

PHARMA QUALITY EUROPE

CSV Process

SPONSOR

- Methodology used to configure/develop the eCRF according to clinical study protocol requirements (i.e. V model)
- Availability of the appropriate specifications (Requirements, Functional Description, Design specification)
- Traceability among specifications
- Compliance with applicable requirements (i.e. 21 CFR Parte 11, Deliberazione n.52 del 24 luglio 2008)

SITE

- Investigator: be informed/be aware

PHARMA QUALITY EUROPE

Testing



• SPONSOR

- Test Plan and procedures for testing
- Test Script (completeness, coherence, traceability)
- Test evidence
- Deviation Management
- Qualification and Independence of Tester and Reviewer

• SITE



Release



• SPONSOR

- Approval flow of eCRF
- Development of guidance for completion management
- Handover of documents
- Deployment of system
- User account activation
- Validation statement
- e-CRF version history



• SITE

- Availability of local installation/validation documents
- Availability of client installation procedures
- Validation statement
- e-CRF version history

Maintenance

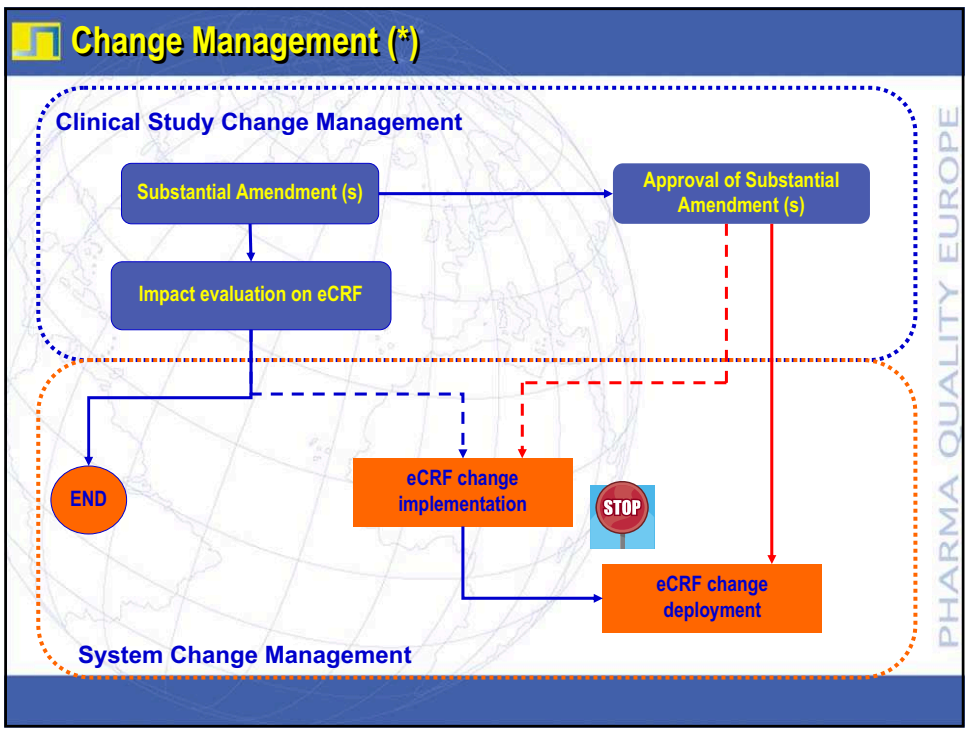
• SPONSOR

- Help Desk
- Availability of the service
- Procedures
 - eCRF Management/Documentation
 - Change Management (*)
 - Security
 - Back up and Restore
 - Disaster Recovery
 - Business Continuity
- Version Tracking

• SITE

- Informed/Trained

PHARMA QUALITY EUROPE



Training

- Training must be executed for:
 - Owner and user
 - Developers
 - Computer operation staff
- Training must include:
 - Training on applicable regulation
 - Job function training
 - SOPs training

Training



• SPONSOR

- Development of training material
- Management of training records
- Training records



• SITE

- eCRF awareness presentation at Investigator Meeting
- Methodology used to train the user on the e-CRF for the clinical trial project
- Training should include system security issues (i.e. good user account management!)
- Documentation that the user account were activate ONLY after training
- Availability of training records (SIV, on going following modification)

Security

- **SPONSOR**
 - Written Procedures for
 1. Physical/Logical protection for the application and database
 2. Password management
 3. Physical protection for server
 4. Backup & Restore
 5. Disaster Recovery
 6. Business Continuity
 - Procedures Implementation
- **SITE**
 - Procedures Implementation
 - Physical protection for the PC
 - Documentation/Records of User Account activation

PHARMA QUALITY EUROPE

Data Entry

- **SPONSOR**
 - Queries Management
- **SITE**
 - SDV
 - Verify chain of events related to a group of data through audit trail
 - Verify that exist a specific access for an external auditor, and in which way is managed
 - Verify what part(s) of the e-CRF have an electronic source
 - Check if patient data and measured values can be entered repeatedly
 - Previous data are altered or deleted without recording in an audit-trail
 - Queries Management

PHARMA QUALITY EUROPE

Usability

• SPONSOR



• SITE

- Adaptability of an eCRF to the routine workflow
- Time required for data entry in the eCRF compared with paper handwritten entries
- Errors due to data entry

TMF Archiving

• SPONSOR



- Procedure for electronic data archiving and maintenance

• SITE



- Procedure for electronic data archiving and maintenance

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Examples of findings (1/2)

- Lack of knowledge from Investigator side
- Inadequate or missing validation of eCRF
- Missing SOPs and documented training
- Unlimited access for the whole personnel of a hospital / outpatient clinic
- Deficient data security
- Missing audit trail
- Previous data altered or deleted without recording in an audit trail

Examples of findings (2/2)

- Data are not adequately secured on the hard disc, e.g. no re-write protection. Manipulation possible
- During transfer of laboratory data, units are changed without previous co-ordination, warning or notification
- Data transfer from the investigator to the host of the system wasn't possible for several days. Potential for data loss
- Data were initially documented on paper print outs. Paper hospital chart, paper-CRF and e-CRF are available. This leads to inconsistencies, more work for the physician, increase of error rate, increase in paper load
- Lack of procedure for long term data archiving and maintenance

Conclusion

- **Ultimate objectives of audits:**
 - Concentrate design and build effort on defining and analyzing e-trial study requirements and specifications
 - Have confirmed systems in place before studies begin
 - Ensure all project start-up and delivery activities are planned in detail and ready before FSFV
 - Ensure all the core project team members understand their roles and responsibilities.
 - Ensure all necessary support will be available to the project when required.
 - Don't make assumptions about investigator sites' e-trial knowledge or capabilities