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Where do auditors see EDC Systems?

- Patient and volunteer data are increasingly often entered and stored in EDC-systems. Outpatient clinic computers or hospital computer systems will more and more substitute the classic paper patient file.
- Commercially developed systems as well as self-programmed systems e.g. support of clinical investigations in Clamp-Studies in Diabetes-Research or psychometric tests.
- During CRO-Audits (e.g. in Clinical Pharmacology units) we see EDC-Systems, which support the study conduct and are used for documentation of data.
- During investigational site audits special systems for data entry (provided by the pharmaceutical company) are evaluated.

- Electronic Records, Electronic Signatures – 21 CFR part 11 – March 1997
- Annex 11 to GMP guide: Supplementary guidelines for computerized systems – 1992
- The application of the principles of GLP to computerized systems – 1995
- Guidance for Industry, Computerized Systems used in Clinical Trials – April 1999.
- FDA Compliance Program Guidance Manual – Compliance Program for Sponsors, Contract Research Organisations and Monitors – October 30, 1998 updated February 21, 2001 and Compliance Program for Clinical Investigators – September 2, 1998
- International Conference on Harmonisation, Good Clinical Practice: Consolidated Guideline – January 1997
- Additional local laws e.g. for Germany: Drug law, data protection law, signature law.

Valid for:



**21 CFR Part
210,211**

**21 CFR Part
58**

**21 CFR Part
50,54,
312,314**

21 CFR Part 11

GMP

GLP

GCP

Applies to all electronic records used to meet GxP requirements, including systems for:

- Batch records, SOPs, test methods, specs, and policies
- Chromatography data systems
- LIMS systems
- Automated document management systems
- Inventory records
- Calibration and preventive maintenance records
- Validation protocols and reports
- Training records
- Customer complaint files
- Adverse event reporting systems

What is an “electric record”?



21 CFR Part 11 – Subpart A, Section 11.3(6)

Definition:

Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.“

- „ ... Electronic records **must be archived** in **electronic** form. The electronic records must be protected to enable their accurate and ready retrieval throughout the relevant retention period ...“
- Keep accurate transcriptions or complete copies of data and „metadata“ on durable media
- Keep links between e-signature and electronic document
- Tighter controls may be required for „open“ systems (encryption & digital sigs)

- Validation
 - Adequate validation including documentation
- User Support
 - Availability of SOPs
 - Adequate training for the user
 - Support “Hotline” of the provider
- Access administration
 - Only authorized persons receive data entry and access rights
 - Identifyable users (User ID, Password)
 - Documentation of system use times
- Data Security
 - Protection against data manipulation, back-ups and contingency plans
 - “Human Readability” of data after system change
- Audit Trail
 - Recording of all data changes in an audit trail
- Data validation / Systemvalidation
 - GAMP validation standard?
 - Definition of entry checks; plausibility checks?

- Definition of functional requirements
- System specification
- Software specifications
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)
- Results and reports for IQ, OQ, PQ
- Final validation report
- User acceptance test and release for use

- Computerized patient charts in hospitals and outpatient clinics currently do not fulfill the regulatory requirements of EDC-systems as they are designed for another purpose (e.g. for health insurance needs).
 - missing audittrail
 - unlimited access for the whole personel of a hospital / outpatient clinic
 - deficient datasecurity
 - missing SOPs and documented training
 - inadequate or missing validation of programs
- Data entry in the computer requires more time compared to handwritten CRF entries. Adaptability of an EDC-System to the routine workflow is limited. Data entry errors may increase.

Findings due to technical issues

- Patient data and measured values can be entered repeatedly. Previous data are altered or deleted without recording in an audittrail.
- On paper printouts the “print date” in stead of the measurement date is printed.
- Saving of entered data was not automated leading to loss of data.
- Data are not adequately secured on the harddisc, e.g. no re-write protection. Manipulation possible.
- During transfer of laboratory data, units are changed without previous co-ordination, warning or notification.

- While the monitor was logged in to the system the investigator couldn't work.
- Data transfer from the investigator to the host of the system wasn't possible several days. Potential for data loss.

Implementation of study protocol in to the EDC-System

- The parallel work on related CRF-pages was not possible. User unfriendly navigation in the e-CRF leads potentially to higher error rate (motivation decreases).
- Data were deleted by the system during review process.
- Computer accepts no calibrated data e.g. from lab devices.
- Pre-defined data checks are not carried out.

Related mistakes following cumbersome data documentation

- Data were initially documented on paperprint 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.
- Manual entry of data by an investigator e.g. from patient diaries leads to increased error rates (the investigator is not a trained datatypist).
Investigators state that they only need 1/3 of time for handwritten documentation compared to electronic entry.

Preparation before use of an EDC-System

- Before using EDC-systems it has to be ensured that regulatory requirements are met. Quality Assurance can add value to this process.
- An upfront detailed definition of requirements and their continuous follow up may avoid complications.
- The procedure of recording of source data in e-trials has to be defined for each center up front.
- The investigator should be freed from manual entry of lab data or QoL questionnaires. Professional double data entry minimizes errors.

Preparation before use of an EDC-System

- Currently investigators see themselves often as datatypists for the sponsor company.
- The study team and the team at the investigator site need intensive training and supervision before implementation of such a system.
- The preparedness to work with such a system also at the investigational site as well as the training to use it is vital and decides about succes or failure. An effective hotline and support is vital.

- EDC-Systems should be able in future to import labdata from various sources.
- The use of EDC systems is currently impeded by problems with portability. Therefor data are not entered directly but have to be documented on paper first. Wireless lans may solve this in the future.
- EDC-Systems will be used more and more frequently in the future. The resources and expenditure needed, especially at the beginning of a trial are tremendous. An enhanced possibility of adaption of such systems to routine clinical practice is needed.