Electronic Source Data in Clinical Investigations and Regulatory Expectations

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Outline

- Computerized systems, Electronic Records & Acceptance of Electronic Data
- 21 CFR Part 11, Regulatory Expectations
- Expectation in GCP Inspections & Data Audits
- Common Problems
- Recommendations/Key Points

Computerized Systems

- They are commonly used in clinical trials to collect and preserve clinical data

- They range from isolated pieces of equipment used to collect/archive clinical data (e.g., a laptop) to complex integrated systems (used by many sites, independent vendor or sponsor)

Users of Computerized Systems

- Clinical Investigators (CIs)
- Sponsors
- Institutional Review Boards (IRBs)
- Study Coordinators (Monitors)
- Statisticians
- Data Managers
- CROs

Electronic Records

- Any combination of text, graphics, data, audio, pictorial, or other information in digital form that is **created, modified, maintained, archived, retrieved, or distributed by a computer system**

Systems to Capture Electronic Records

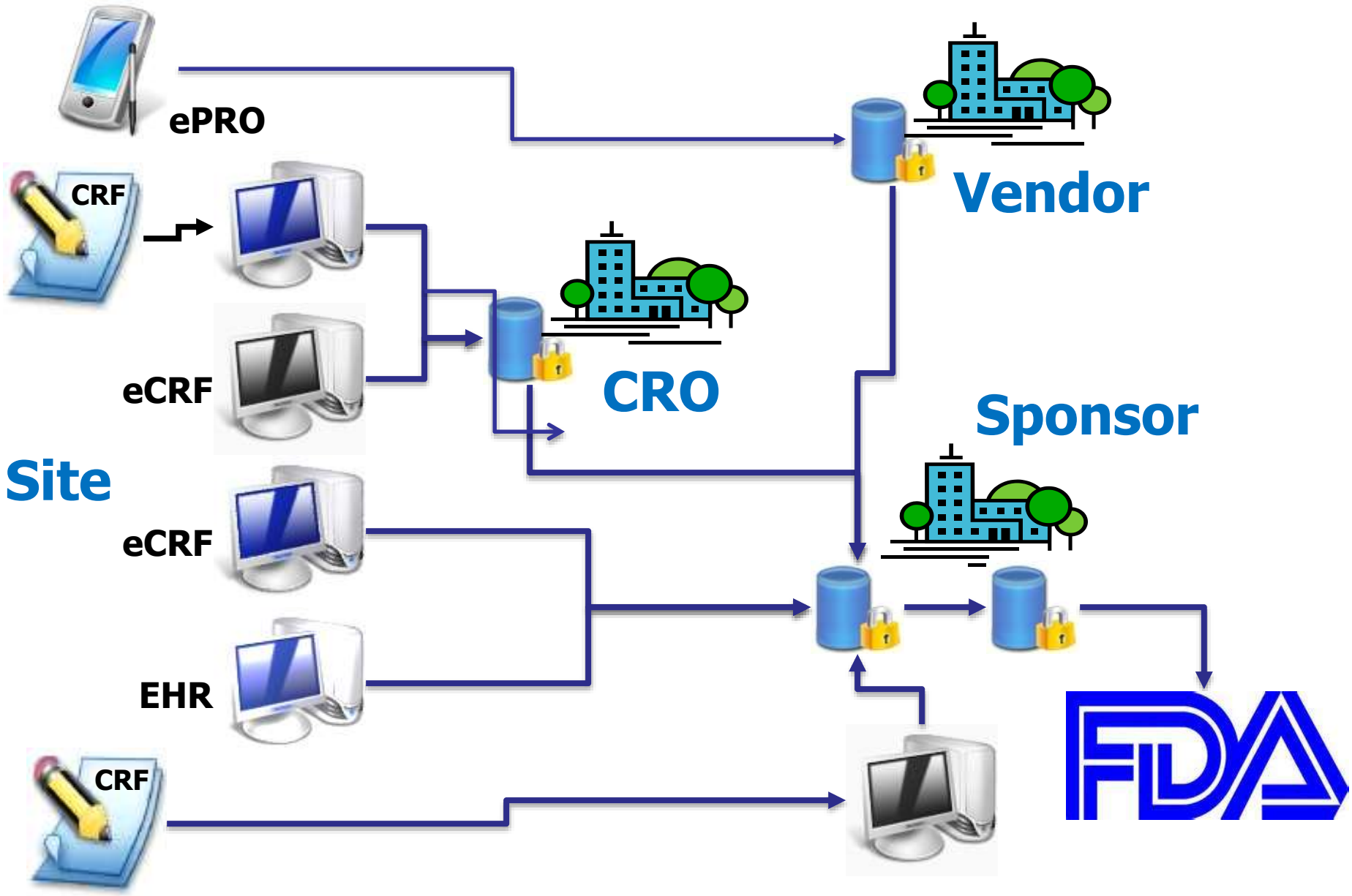
- Electronic Case Report Forms (eCRFs)
- Electronic Patient Reported Outcomes (ePRO)
- Interactive Voice Response System (IVRS)
- Adverse Event Reporting Systems (AERS)
- Laboratory Information Management Systems (LIMS)
- Systems that automatically record data by integrating data from a medical device such as an ECG, Holter- Monitor, MRI, etc…

FDA's Acceptance of Electronic Source Data

- Electronic data must meet the same fundamental elements of data quality (e.g. attributable, legible, contemporaneous, original, & accurate) and integrity (complete and consistent) expected of paper records

- Acceptance of data from clinical trials for decision-making purposes depends on FDA's ability to verify the quality & integrity of the data

Electronic Data Flow



21 CFR PART 11, REGULATORY EXPECTATIONS

21 CFR Part 11

- Establishes the requirement under which the FDA accepts **electronic records** & electronic **signatures** as equivalent to paper-based records & handwritten signatures

- It permits verification that information submitted to the Agency accurately represents the original source data, even when collected electronically

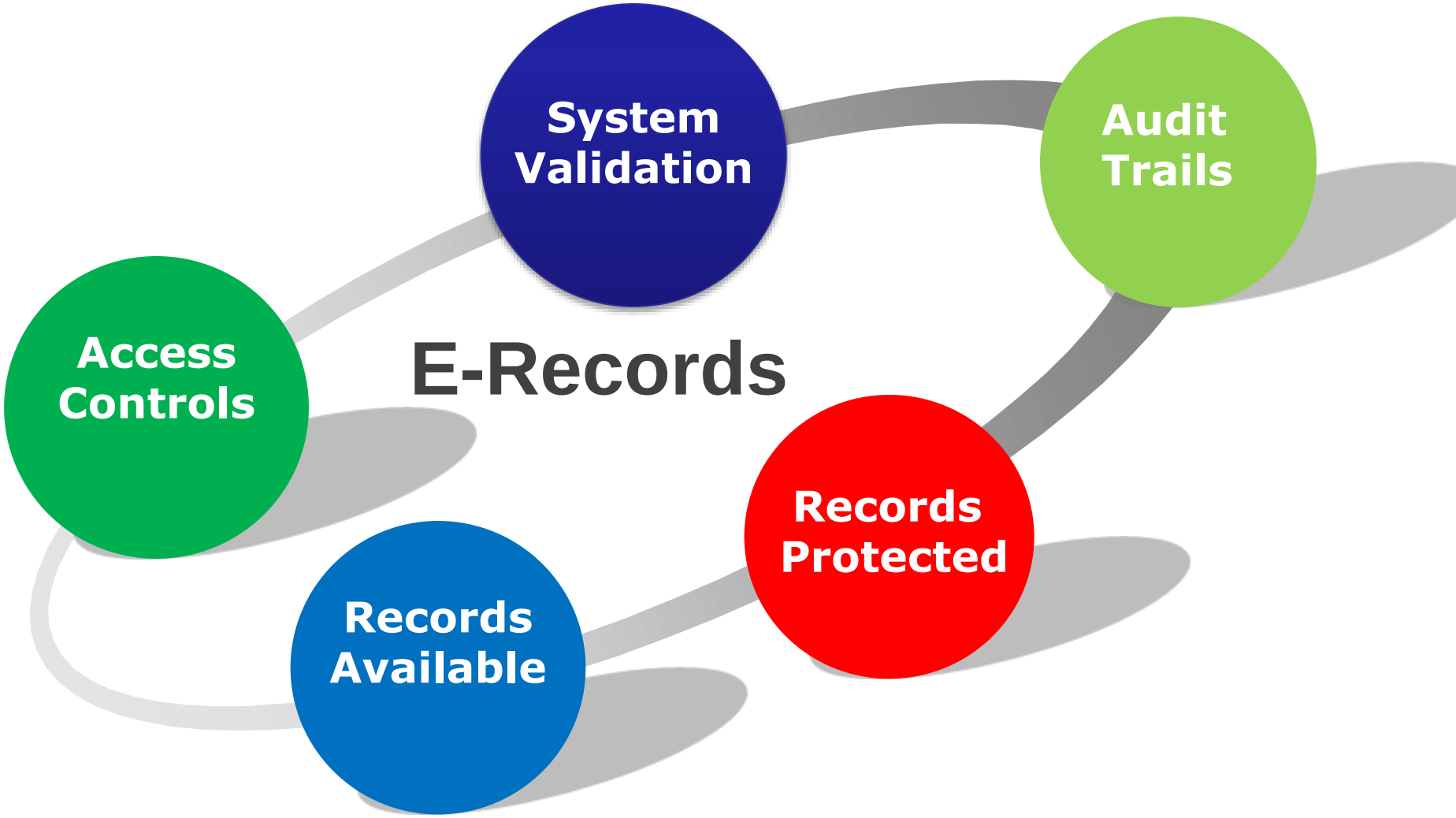
- Went into effect August, 1997

21 CFR Part 11 (cont.)

- Part 11 describes the technical & procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures.

- Part 11 is a companion regulation to other FDA regulations and laws called "predicate rules," where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed

Required Procedures and Controls



System Validation

- "…Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records…."

Access Controls: Internal Security Safeguards

- Access must be limited to authorized individuals
- Each user should have an individual account/password
- Passwords should be changed at established intervals
- The system should limit and record the number of unauthorized log-in attempts
- Automatic log off for long idle periods

Records Protected: External Security Safeguards

- Protection of records to enable their accurate and ready retrieval throughout the records retention period.

- Controls should be established to:
  - Prevent unauthorized external accesses a altering (e.g.-firewalls, anti-spy, etc…)
  - Prevent, detect, and mitigate effects of computer viruses, worms etc.

Audit Trails

- Computer-generated, **time-stamped** electronic audits trails are the preferred methods for tracking changes to electronic source documentation
- Audit trails used to capture electronic record activities should describe **when**, by **whom**, and the **reason** changes were made
- Ensure that audits cannot be overridden

Records Available

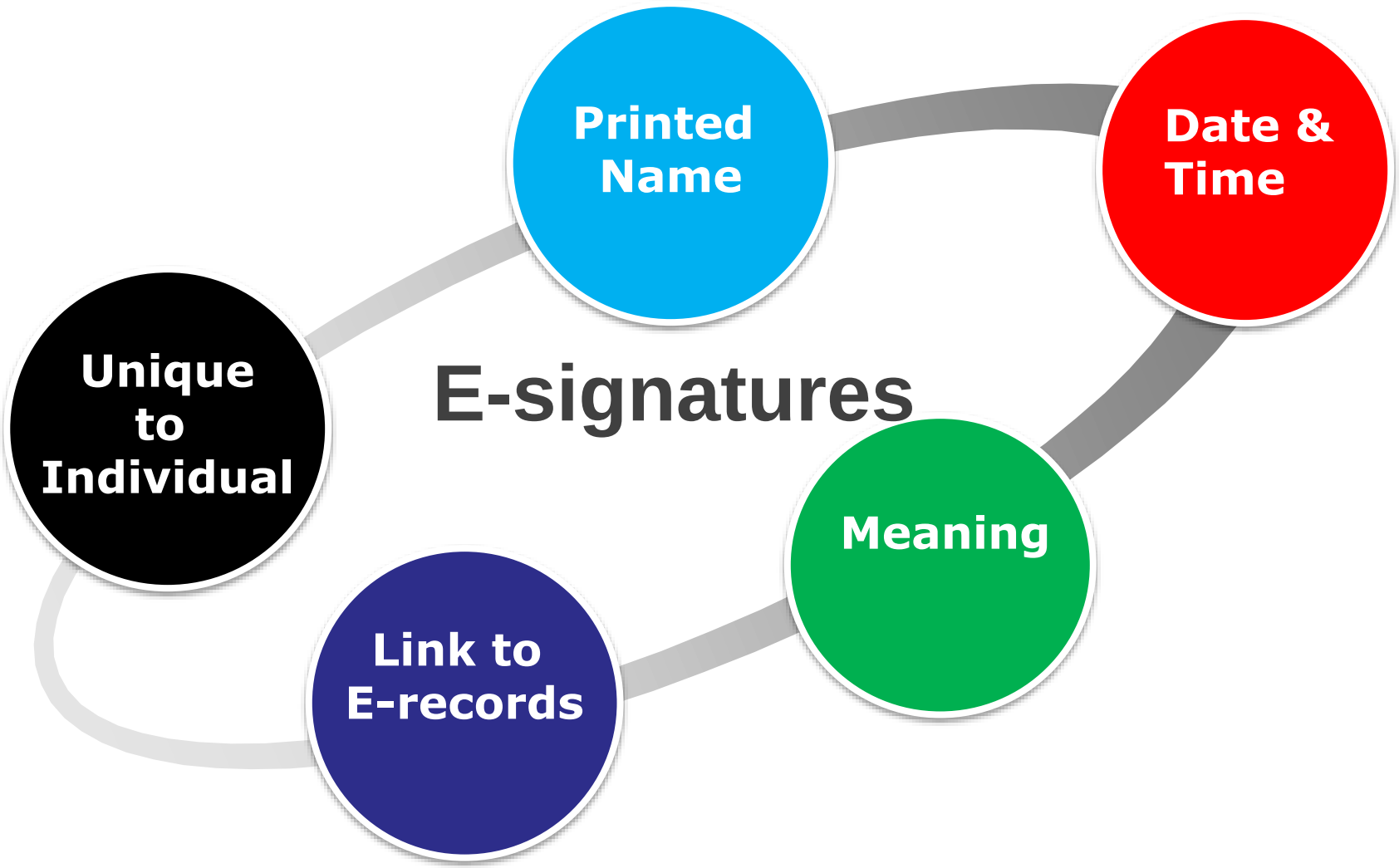
- When original observations are entered directly into a computerized system, the electronic record is the source document

- Clinical investigators must **retain records** required to be **maintained** for a period of time specified in the FDA's regulations

Study Protocols and Training

- Protocols should identify steps at which computerized system will be used to create, modify, maintain, archive, retrieve or transmit source data
- All personnel who develop, maintain, or use the computerized systems should be trained on how to perform assigned tasks
- Document the computer education, training, and experience

Signature Manifestations



Signature Manifestations

- Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
  1. The **printed name of the signer**
  2. The **date and time** when the signature was executed; and
  3. The **meaning** (such as review, approval, responsibility, or authorship) associated with the signature

Electronic Signature /Record Linking

- Electronic signatures & handwritten signatures executed to electronic records shall be **linked to their respective electronic records** to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means

- Each electronic signature shall be unique to one individual

EXPECTATION IN GCP INSPECTIONS & DATA AUDITS

Bioresearch Monitoring Program Inspection of EDC

- The same inspectional objectives as in inspecting paper records to determine:
  - the integrity of efficacy & safety data
  - whether the rights, safety and welfare of subjects were protected
  - that FDA regulated research is conducted in compliance with applicable regulations

Inspection Expectations

- Records must be **preserved** to meet regulatory requirements
- **Available** for FDA inspection and copying
- **Retained** for appropriate length of time
- **Independently preserved at clinical site** and/or some other designated site (e.g., technology provider)

Expected Controls

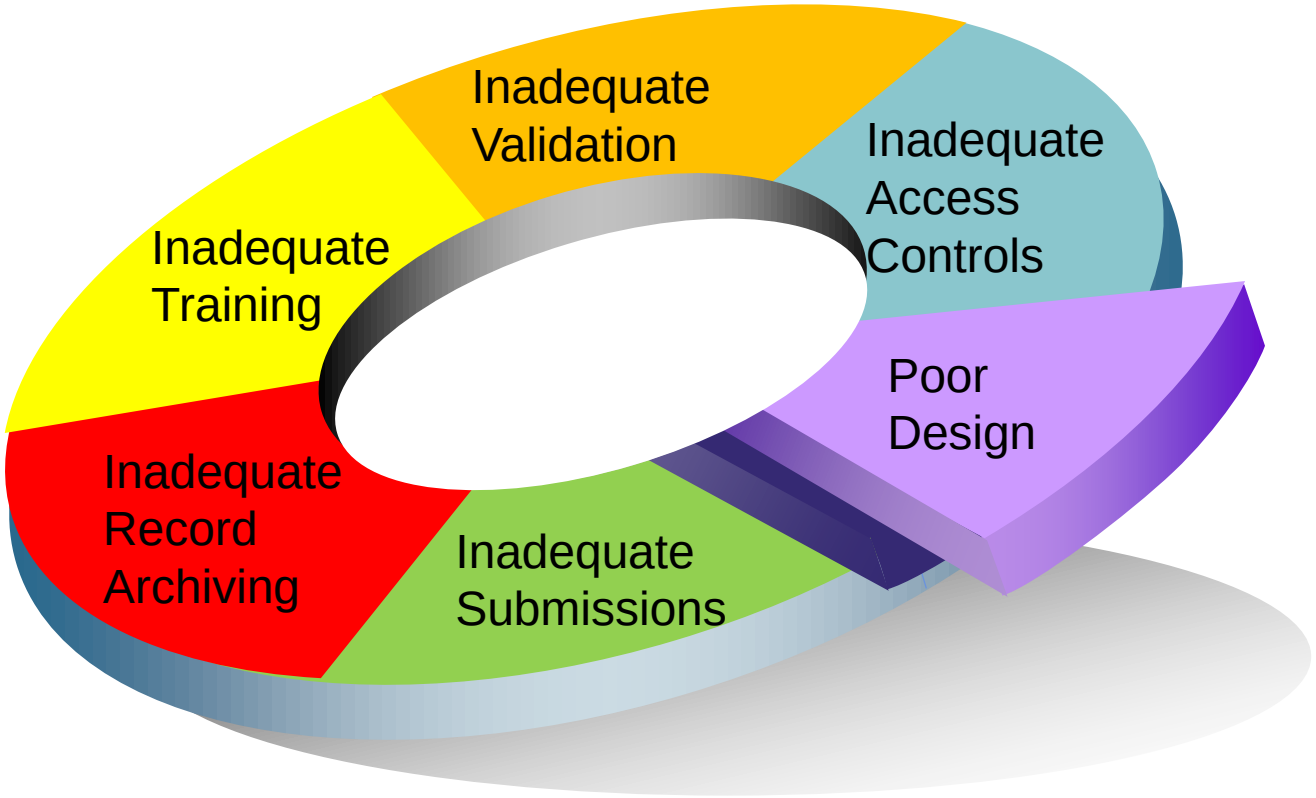
- **Access must be limited** to authorized individual
- A firm should utilize **password protected**, individual accounts; tokens; biometrics for trained employees
- System features should **limit access** attempts and idle periods

Validation

- A firm needs to assess and document its decision as to **what** *and* **when** to validate
- Remember predicate rules (accurate/adequate case histories)!
- Changes that exceed previously established operational limits or design specs should be validated
- Effects of changes should be evaluated and validated, based on a **risk-based assessment**

COMMON PROBLEMS

Common Problems



Examples of Significant Observations

- Firm uses Microsoft Windows ™ **log in credentials for computers** that are machine specific and therefore not unique for each user. User identity regarding access to computer and possible source data changes cannot be reconstructed.

- A study coordinator leaves employment at a Clinical Investigator site. The new study coordinator uses the **prior coordinator's login** and password to access and enter/modify data in a sponsor-provided system.

- If the firm uses eCRF to capture patient data without any paper copies generated and **changes to the eCRF are not tracked** including what was changed, who changed it, when, and why it was changed, then the integrity of the data are not reliable.

RECOMMENDATIONS/KEY POINTS

Recommendations

- Utilize appropriate controls to ensure that e-records/data and electronic signatures are ***trustworthy, accurate, and complete***
- Use appropriate controls to ensure that clinical data are ***protected*** so that study related activities *can be reconstructed*
- Use a ***risk-based approach*** for designing/utilizing computerized systems for clinical data
  - flexible regulations support a risk based approach (e.g., case history, monitoring)

Key Points

- Requirements for clinical data **do not change** for paper, computer, or hybrid approaches
- Computerized systems should meet all regulatory requirements with the same degree of confidence as that provided with paper systems
- Records must comply with the underlying predicate rules

References

- Part 11 regulation
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11
- Part 11 Scope and Application Guidance
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126953.pdf
- Computer Systems Used in Clinical Investigations
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

Thank You!

Questions?

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