Electronic Source Documentation in Clinical Investigations

Sean Y. Kassim, Ph.D.

CDER Small Business Assistance – Webinar

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Overview

1. FDA’s Part 11 Regulation
2. Part 11 Guidance
3. Regulatory Challenges
4. Inspection Expectations
5. Draft eSource Guidance
FDA’s Part 11 Regulation
E-Record and E-Signatures
What is Part 11?

• FDA regulation describing requirements for maintaining FDA-required records and signatures in electronic form

• Requirements are intended to ensure the integrity, validity and trustworthiness of e-records and e-signatures

• Regulation went into effect August 1997
Key Elements - 21 CFR 11.10

- Access Controls
- System Validation
- Audit Trails
- Records Protected
- Records Available
- E-Records
E-signature controls
- Signature/record linking
- Signature manifestations/purpose (*review/approve/verify*)
- Access Controls
  - Distinct password (or biometric) protected user account
  - Used only by genuine owners
  - Password and token protections utilized (checked, revised, etc.)
- FDA Certification
- Written Policies – SOP describing how signatures are assigned and used
- Employee Training
Part 11 Guidance and FDA’s Current Enforcement Policy

- Computerized Systems used in Clinical Investigations (May 2007)
- Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Dec 2009)
### Key Components

- **Fewer Records**
  - Fewer records subject to Part 11 controls

- **Enforcement Discretion**
  - FDA does not intend to take action under certain conditions

- **Other Regulations**
  - FDA will enforce predicate rules (21 CFR 312, 812, 50, 56, etc)

- **Risk Approach**
  - Firms can use a risk-based approach for Part 11 controls
Fewer Part 11 Records

• “Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations.”

• “Part 11 also applied to electronic records submitted to the Agency under the FD&C Act and the Public Health Service Act even if such records are not specifically identified in Agency regulations”

• “Records that are not required to be retained under predicate rules but that are nonetheless maintained in electronic format, are not part 11 records.”
Electronic Records that Remain in Scope

- “Records that are required to be maintained under predicate rules are maintained in electronic format in place of paper format.”

- “Records that are required to be maintained under predicate rules, that are maintained in addition to paper format, and that are relied on to perform regulated activities.”

- “Electronic signatures that are intended to be the equivalent of handwritten signatures, initials and other signings required by predicate rules.”
Enforcement Discretion

• “We (FDA) do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11”

• “However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.”
Risk-Based Approach to Part 11

- Firms (e.g., sponsor, CI, IRB, CRO) decide *when* and *to what extent* the following controls need to be utilized based on a *documented risk assessment*
  - Validation of computerized system (software, firmware, hardware)
  - Audit trails that document who/what/when/why records were created/modified (computer generated, other procedures)
  - Access Controls (e.g., use passwords, biometrics)
  - Electronic record preservation (paper, electronic, etc.)
• “Certified copy” - copies of records must be generated using a verified process that produces copies with same content and meaning as original record (see CPG # 7150.13)

• If a firm has the ability to search, sort or trend records, copies made available to FDA must preserve this same capability

• Other parts of part 11 remain intact!
• Computerized Systems used in Clinical Investigations (2007) – Audit trails, record retention

• Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (2009) – ePRO
May 2007 Guidance on Computerized Systems Used in Clinical Investigations

Recommendation Categories

• Training of Personnel
• Internal/ External Security Safeguards
• Source Documentation and Retention
• Audit Trails
• Other System Features
• Standard Operating Procedures
Training

• All personnel who develop, maintain, or use the computerized systems should be trained
• Personnel must learn how to perform their assigned tasks
• Document the computer education, training, and experience
Internal Security Safeguards

- Access must be limited to authorized individuals
- Each user should have an individual account
- 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
External Security Safeguards

Controls should be established to:

• Prevent unauthorized external software applications from altering, browsing, querying, or reporting data

• Prevent, detect, and mitigate effects of computer viruses, worms, or other potentially harmful software code on study data and software

(e.g.-firewalls, antivirus, anti-spy, etc...)
• When original observations are entered directly into a computerized system, the electronic record is the source document.

• Under 21 CFR 312.62, 511.1(b)(7)(ii) and 812.140, the clinical investigator must retain records required to be maintained under part 312, § 511.1(b), and part 812, for a period of time specified in these regulations.

• Applies to the retention of the original source document or a copy of the source document.
Audit Trails

- Computer-generated, time-stamped electronic audits trails are the preferred method for tracking changes to electronic source documentation.
- Audit trails or other security methods used to capture electronic record activities should describe when, by whom, and the reason changes were made to the electronic record to ensure that only authorized additions, deletions, or alterations have occurred.
- Ensure that audits cannot be overridden.
Regulatory Challenges

• 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.
General Suggestions

• 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)
Risk Management Principles

Risks in Clinical Trials

Harm to Subjects
- Incorrect information can harm subjects

Subject Rights
- Unlimited access compromises confidentiality

Data Quality and Integrity
- Compromise via unapproved changes
Electronic Health Records and Clinical Research

- Must maintain requirements of predicate rules

- Controls such that data is accurate, legible, contemporaneous, original, attributable

- If eHR is used to directly populate eCRF, it must be made available for inspection – and adequately controlled for study reconstruction
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)

• Audit trails are not explicitly required in GCP/HSP regulations; however to reconstruct study, we need these details
Expected Controls

- Access must be limited to authorized individual [21 CFR 11.10(d)]

- 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
Draft eSource Guidance

Electronic Source Documentation in Clinical Investigations
FDA Draft Guidance Overview

DRAFT Guidance Overview

• Defining Electronic Source (eSource) Data & Documentation with common examples
  – Data Elements & Data Element Identifiers

• Electronic creation, modification, transmission, and storage of eSource (3 Tiers of Data)

• Investigator Responsibilities for review, archiving, and transmission of eSource clinical data
  – Data Integrity & Communication with Sponsor

• Information Sponsors should provide as part of protocol, investigational plan, and site inspections
Definition of eSource

- *eSource documents* and *eSource data* are used to describe source documents and source data for which the original record and certified copies are initially captured electronically
  - eCRFs
  - ePRO
  - Data initially documented in an EHR
  - Electronically generated lab reports
  - Medical Images
A data element in an eCRF represents a single observation associated with a subject in a clinical study

- Blood Pressure
- BMI
- WBC Count
- Pain Measurement
Data Element Identifiers

- *Data element identifiers* are those attributes that identify:
  - The originators of data elements, including those entered manually (e.g., by the investigator), and automatically (e.g., from a device or instrument)
  - The date and time the data elements are entered into the eCRF
  - The study subject to which the data elements belong.
<table>
<thead>
<tr>
<th>Field in CFR</th>
<th>Data Element</th>
<th>Data Element Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID#</td>
<td>AD0012</td>
<td>Randomization algorithm in central computer/June 1st, 2008/3.00 pm AD0012</td>
</tr>
<tr>
<td>Sex</td>
<td>male</td>
<td>*Investigator Dr R Smith/June 1st, 2008/10.53 am AD0012</td>
</tr>
<tr>
<td>Age</td>
<td>25 years</td>
<td>*Investigator Dr R Smith/June 1st, 2008/10.53 am AD0012</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>15.3 g/l</td>
<td>Co-op labs/June 2nd, 2008/12:06 pm AD0012</td>
</tr>
<tr>
<td>Date blood was drawn for Hemoglobin determination</td>
<td>June 1st, 2008</td>
<td>*Investigator Dr R Smith/June 1st, 2008/10.53 am AD0012</td>
</tr>
<tr>
<td>Radiological report</td>
<td>“Right upper lobe consolidation”</td>
<td>Dr P Brown, radiological associates/ June 1st, 2008/4.12 pm AD0012</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>124/88</td>
<td>*AB instrument systems/ June 1st, 2008/10.53 am AD0012</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>**Lasik 40mg QD</td>
<td>Investigator Dr R Smith/June 1st, 2008/10.53 am AD0012</td>
</tr>
</tbody>
</table>
Three Tiers of Data

- Tier 1: Data Entry
- Tier 2: Data Review
- Tier 3: Data Processing and Transmission
Investigator Responsibilities

- The eCRF should permanently carry the electronic signature of the investigator who reviewed it.
- The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review & sign off
  - Make available for purposes of an FDA inspection.
- When an investigator has transcribed data elements from paper documents into an eCRF, the investigator must also retain the paper documents for review by FDA.
Sponsor Responsibilities

- Protocol should include information about the intended use of computerized systems during the conduct of a clinical study
  - Description of the security measures employed to protect the data
  - Detailed diagram and description of the transmission of electronic data
- Describe electronic tools intended to be used to detect events in the eCRF such as, but not limited to, data inconsistencies, missing data, and entries out of range
References

• Preamble to 21 CFR 11
  – http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?position=all&page=13430&dbname=1997_register

• Part 11 regulation

• Part 11 Scope and Application Guidance

• Computer Systems Used in Clinical Investigations
Contacts

Part 11 Work Group Members-
- Sean Kassim – Clinical and Bioanalytical Drug Contact
  • sean.kassim@fda.hhs.gov
- George Smith
  • george.smith@fda.hhs.gov
- Jonathan Helfgott
  • Jonathan.helfgott@fda.hhs.gov
- Brian Belz
  • Brian.belz@fda.hhs.gov
- Vernon Toelle-Animal Drug Contact
  • vernon.toelle@fda.hhs.gov
- John Murray-Device Contact
  • john.murray@fda.hhs.gov
- Joseph (Dave) Doleski
  • joseph.doleski@fda.hhs.gov

Thank you for your time