
FDA Regulations and Guidance on Software Used in Clinical Trials

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The Challenge Faced By the FDA

How does the FDA fulfill it's mandate to promote and protect public health if "electronic records" are the only records available for FDA reviews and audits?

For "direct data entry" how will the FDA be able to ascertain:

- The accuracy of the data?
- Attribute the data to an observer?
- Determine whether data have been altered?

Challenges for Direct Data Entry

- Local certified copy for FDA review and copying.
- Local time stamps on electronic records.
- Audit trail immutable and available for local review and copying.
- Irrefutable Authentication, Session control
- Training for those who develop, use or maintain the system.
- Revision and change control procedures and documentation.

Regulations & Guidances

21 CFR Part 11

- Binding set of US federal regulations.
- Electronic records and signatures.
- Focus on direct data entry at clinical sites.

Guidance for Industry: Computerized Systems Used in Clinical Trials

- FDA's current thinking
- Focus on direct data entry

21 CFR Part 11

Electronic Records and Signatures

www.fda.gov/cder/esig/part11.htm

www.fda.gov/ora/compliance_ref/bimo

Effective Aug. 20, 1997

“... set forth criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable and generally equivalent to paper records and handwritten signatures executed on paper.” – 11.1 Scope (a)

21 CFR Part 11 - Scope

“This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations.” – 11.1 Scope (a)

Is a DataFax CRF Image an Electronic Record?

“However, this part does not apply to paper records that are, or have been, transmitted by electronic means.” – 11.1 scope (b)

“The agency does not intend part 11 to apply to paper records even if such records are transmitted or received by fax.” – Supplementary information 21. Page 13437

Guidance for Industry

Computerized Systems Used In Clinical Trials

- www.fda.gov/ora/compliance_ref/bimo
- Final version: April 1999
- FDA's current thinking, not an enforceable regulation.

Guidance - Objectives

“FDA’s acceptance of data from clinical trials for decision-making purposes is dependent upon its ability to verify the quality and integrity of such data during its onsite inspections and audits.

To be acceptable the data should meet certain fundamental elements of quality whether collected and recorded electronically or on paper.”

Fundamental Elements of Quality

- Attributable
“... traceable to individuals responsible for observing and recording the data.”
- Original
- Accurate
- Contemporaneous
- Legible

Definitions

“Direct Entry means recording data where and electronic record is the original capture of the data.”

The Guidance - Scope

“Although the primary focus of this guidance is on computerized systems used at clinical sites to collect data, the principles set forth may also be appropriate for computerized systems at contract research organizations, data management centers and sponsors.”

General Principles A-K

- A. “Each study protocol should identify at which steps a computerised system will be used to create, modify, maintain, archive, retrieve, or transmit data.”
- In a DataFax study original data are created, modified, etc. using paper CRFs.
 - DataFax is used to collect, transcribe and process a copy of the original data, and to manage quality control procedures.

General Principles A-K

- B. “... documentation should identify what software and, if known, what hardware is to be used in computerized systems that create, modify, archive, retrieve, or transmit data.”
- In a DataFax study no computerized system is used at clinical sites to create data.
 - Describe software (including DataFax) and hardware used for internal data management.

General Principles A-K

- C. "Source documents should be retained to enable a reconstruction and evaluation of the trial."
- CRFs need to be retained at the clinical sites for FDA onsite reviews and audits.

General Principles A-K

- D. "When original observations are entered directly into a computerized system, the electronic record is the source document."
- Not applicable in DataFax studies.

General Principles A-K

- E. “The design of a computerized system should ensure that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper systems.”
- For purposes of FDA onsite reviews DataFax is a “paper system”.

General Principles A-K

- F. “Clinical investigators should retain either the original or a certified copy of all source documents sent to a sponsor or contract research organization, including query resolution correspondence.”
- Use patient / page option for QC reports and file with patient CRFs.

General Principles A-K

G. “Any change ... should not obscure the original information. The record should clearly indicate that a change was made and clearly provide a means to locate and read the prior information.”

- Keep secondary records / CRFs
- Resolve, don't delete, QC notes.

General Principles A-K

H. “Changes to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e). Documentation should include who made the changes, when, and why they were made.

- Use internal QC notes to document why a change was made if the change is not already apparent on the CRF.

General Principles A-K

J. “Data should be retrievable in such a fashion that all information regarding each individual subject in a study is attributable to that subject.”

- Use a single patient ID number, not separate screening and study numbers.

General Principles A-K

K. “Computerized systems should be designed: (1) So that all requirements assigned to these systems in a study protocol are satisfied.”

- Do not specify software requirements in the protocol which you know are not met by your software (e.g. DataFax does not currently allow you to restrict viewing of specified plates).

General Principles A-K

- K. “Computerized systems should be designed: (2) to preclude errors in data creation, modification, maintenance, archiving, retrieval, or transmission.”
- Use DataFax features which help to eliminate errors (e.g. edit checks).
 - Report any problems to CDSI at support@datafax.com

System Features

- “Systems used for direct entry of data should include features that will facilitate the collection of quality data. Features that automatically enter data into a field when that field is bypassed should not be used.”
- Only use DataFax skip patterns in-line.
 - Edit checks that enter values may be written to ask for confirmation.

Software Validation

Systems Used to Create Electronic Records:

- require design level software validation

Systems Used for in house data management:

- require functional testing and documentation

Example:

- MS Access OK in-house but not for RDE

System Dependability

“In the special case of database and spreadsheet software that is

- (1) Purchased off-the-shelf,
- (2) Designed for and widely used for general purposes,
- (3) Unmodified, and
- (4) Not being used for direct data entry

the sponsor or contract research organization may not have documentation of design level validation. However, the sponsor or CRO should have itself performed functional testing.”

Design Level Software Validation Documentation

- “Written design specifications”
- “A written test plan based on the design specifications”
- “Test results and an evaluation of how these results demonstrate that the predetermined design specification has been met.”

Relevant Regulations and Guidances

- FDA GMP/GLP/GCPs
- Compliance Program 7348.808 - GLPs (8/94)
- 21 CFR Part 11 (8/97)
- Compliance Program 7348.810 - Sponsors, CROs and Monitors (10/98)
- Guidance for Industry: Computerized Systems Used in Clinical Trials (5/99)
- Enforcement Policy: e-Records; e-Signatures - Compliance Policy Guide (7/99)