Guidance for Industry

Electronic Source Documentation in Clinical Investigations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Leonard Sacks at 301-796-8502.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

December 2010

Guidance for Industry

Electronic Source Documentation in Clinical Investigations

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and
Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800
E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
and/or
Division of Small Manufacturers, International, and
Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850
Tel: 800-638-2041
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
and/or
Office of Critical Path Programs, Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 32, rm. 4173
Silver Spring, MD 20993-0002
Tel: 301-796-8490

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

December 2010

TABLE OF CONTENTS

Guidance for Industry[1]
Electronic Source Documentation in Clinical Investigations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to sponsors, contract research organizations (CROs), data management centers, and clinical investigators on capturing, using, and archiving electronic data in FDA-regulated clinical investigations. This guidance is intended to ensure the reliability, quality, integrity, and traceability of electronic source data and source records maintained at the site for FDA inspection.

This guidance is intended to promote the capture of source data in electronic form, which will help to:

- eliminate unnecessary duplication of data,
- reduce the opportunity for transcription errors,
- promote the real-time entry of electronic source data during subject visits, and
- ensure the accuracy and completeness of data (e.g., through the use of electronic prompts for missing or inconsistent data).

This guidance is intended to be used together with the guidances for industry [2] entitled:

- *Computerized Systems Used in Clinical Investigations*
- *Part 11, Electronic Records; Electronic Signatures – Scope and Application*
- *General Principles of Software Validation; Final Guidance for Industry and FDA Staff*

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Office of Critical Path Programs, the Good Clinical Practice Program, and Bioresearch Monitoring Program Managers for the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] FDA guidances are available on FDA's Web page at www.fda.gov/RegulatoryInformation/Guidances/default.htm. FDA guidances are issued and updated regularly. We recommend you check the Web site to ensure that you have the most up-to-date version of a guidance.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The initial documentation of data in a clinical study is considered *Source* documentation or *Source* data. The originator, or recorder, may document the data either on paper or electronically. Source data documented in paper format (paper source document) is a tangible document that can be physically located at a clinical study site and readily available for inspection and copying by FDA investigators.

With the increasing use of computerized systems in clinical studies, it is common to find at least some source data documented electronically (eSource document). Common examples include clinical data initially documented in electronic health records maintained by hospitals and institutions; electronic case report forms (eCRF), which are increasingly being used by clinical study sponsors; electronically generated laboratory reports; electronic medical images from devices; and electronic diaries provided by study subjects. The use of eSource documentation is of great value in the conduct of clinical studies. However, unlike paper source documents, eSource documents and data can be easily copied, transferred to other computerized systems or devices, changed, or deleted without obvious evidence of these events.

Access to source documents and source data is essential to inspection and review of clinical studies and inspection of clinical study sites. Verification of source data is necessary to confirm, among other things, the participation of subjects and to detect omissions, transcription errors, alterations in data, or falsification of data. When paper source documents are available for review, tracing of data in paper-based studies can be performed easily. However, when source data are electronic, the data are traced through complex data capture, transmission and archival processes.

This guidance recommends practices that will help ensure that electronic source data are accurate, legible, original, attributable (e.g., user name and password), and contemporaneously entered; and meet the regulatory requirements for recordkeeping and record retention.[3]

This guidance discusses the following specific topics related to electronic source data:

- The identification of the *data element* as the basic unit of information in the eCRF
- The description of the source of each data element

[3] Investigators are required to maintain adequate and accurate case histories that record all observations and other data pertinent to an investigation under 21 CFR 312.62(b) and 21 CFR 812.140(a). Investigators of device studies must maintain the study records during the investigation and for a period of two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application. 21 CFR 812.140(d). Investigators of drug studies must retain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. 21 CFR 312.62(c).

- Information about the electronic creation, modification, transmission, and storage of source data and documents
- Investigator responsibilities with respect to reviewing and archiving data
- Transmission of data to the sponsor and/or other designated parties
- Preservation of data integrity

III. ELECTRONIC SOURCE DOCUMENTS AND SOURCE DATA

FDA regulations define an *electronic record* as any combination of text, graphics, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system (21 CFR 11.3(b)(6)).

The terms *eSource* documents and *eSource* data are not defined in FDA's regulations. For the purpose of this guidance, the terms *eSource documents* and *eSource data* are used to describe source documents and source data for which the original record and certified copies[4] are initially captured electronically. eSource documents and eSource data can come from a variety of activities and places. For example, study personnel may perform a direct entry of clinical data into a computerized study database. eSource data may be collected from a subject's electronic health record, which is maintained by clinical study staff. eSource data also can come from an electronic diary, maintained by a study subject or from an automated instrument that records and stores a subject's biological readings.

The eCRF is a vehicle used to assemble all the data from different electronic- and paper-based systems and makes it possible to capture and organize these diverse data in a manner that satisfies the study protocol and that enables the data to be systematically reviewed and analyzed by investigators, other authorized parties, and FDA (e.g., during FDA inspections).

Figure 1 depicts one example of how data might flow in a clinical study from the point of data entry into an eCRF, and eventually into a tabulation prepared by the sponsor and submitted to FDA in support of a marketing application. In figure 1, three tiers of data management are identified: Tier 1-Data Entry; Tier 2-Data Review; and Tier 3-Data Processing and Transmission. As illustrated in figure 1, data from paper-based or computer-based systems can ultimately be preserved in the eCRF as electronic data.

[4] See Glossary of Terms in this document.

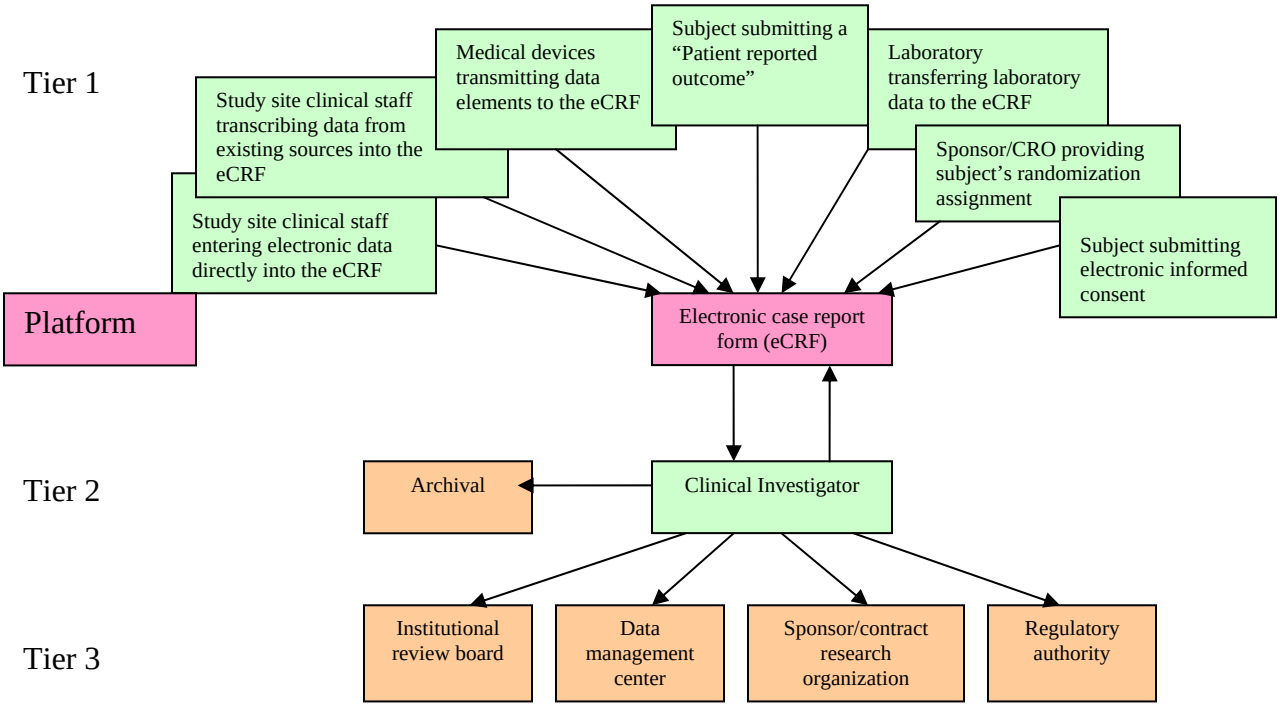

Figure 1: Assembly and processing of data elements using the eCRF as a platform

Tier 1 (Data Entry): Tier 1 represents examples of various categories of data *originators*, those responsible for creating the data elements in a clinical study (e.g., the clinical investigator, study site clinical staff, medical devices, and subjects; see section III.A of this document for further discussion). Original observations can be entered directly into the eCRF or transmitted to the eCRF from various locations, devices, or instruments. Source data could be collected and documented initially on paper and transcribed into an electronic system or documented initially electronically (i.e., direct entry).

Associated with each of these categories is a list of authorized data originators (e.g., the category Patient Reported Outcome may contain a list of all the subjects providing a patient reported outcome). Each of these authorized data originators would have an individual identifier (e.g., user name and password) that enables him/her to electronically enter specific data elements into the system.

Tier 2 (Data Review): Once the data elements have been integrated into an eCRF, the clinical investigators, who are ultimately responsible for conducting or personally supervising the conduct of a study,[5] can review the eCRF. Investigators thus have the opportunity to review completed portions of the eCRF, to query the originator prior to transmission to the sponsor and

[5] See 21 CFR 312.3(b) and 812.3(i).

other parties regarding data elements that raise concerns, and ensure that any relevant clinical issues raised by the data are addressed. Once investigators have reviewed and signed off on completed portions of the eCRF for a study subject, the data can be archived and transmitted to the parties in Tier 3.[6]

Tier 3 (Data Processing and Transmission): These are parties responsible for study data management who may receive the data once the investigators have signed off (e.g., the institutional review board, sponsor).

Certain individuals can operate at more than one Tier. For example, the investigator could enter data at Tier 1 as *study site clinical staff*, view subject data and sign off on eCRFs at Tier 2 as *investigators*, and analyze and report data as an *investigator/sponsor* at Tier 3.

The following sections describe in more detail the data that are captured or managed at each Tier level.

A. Tier 1 - Data Entry[7]

1. Data Elements

A data element in an eCRF represents a single observation associated with a subject in a clinical study. Examples include birth date, white blood cell count, pain severity measurement, or other clinical observation made and documented during a study.

For each data element provided on a subject in a clinical study, there is an originator responsible for its entry into the eCRF (see section III.A.2 of this document).

a. New Data Elements Created by Authorized Originators

Many data elements in a clinical study are newly created at a study visit and may be entered directly into the eCRF by an authorized data originator (e.g., blood pressure, weight, temperature, pill count, resolution of a symptom or sign). FDA may sometimes request other documents to corroborate a newly created data element entered directly into the eCRF by an authorized originator. For example, in an initial visit, an investigator may ask a subject about underlying illnesses such as diabetes, and proceed to enter *diabetes* in a section on underlying illnesses. FDA may request a hospital record to review for evidence of blood glucose testing or the use of anti-diabetic agents to corroborate a diagnosis of diabetes.

[6] Under exceptional circumstances, a protocol may require the blinding of an investigator to specific data elements. For example, a measurement of urine osmolality could effectively unblind the treatment allocation for an osmotic diuretic. In such protocol-specified situations, a party in Tier 1 would be able to transmit a data element directly to a party in Tier 3 without the investigator's sign off.

[7] Consistent with the principles of the International Conference on Harmonisation, "E6 Good Clinical Practice: Consolidated Guidance," which is available on the FDA guidance Web page.

The accuracy of data elements that are transferred automatically from a medical device or instrument to the eCRF (e.g., a laboratory measurement of hemoglobin, an EKG, or an automated measurement of blood pressure) depends on the ability of the equipment to record and transmit data from the device or instrument to the eCRF. FDA may ask the sponsor and/or investigator during an inspection for information on the reliability and integrity of the software and equipment used to record and transmit the data element, and the ability of the software to ensure that data elements are entered for the correct subject.

b. Transcription of Data Elements from Other Source Documents

Data elements that are transcribed by an individual from a source document, such as a laboratory report or hospital record, into an eCRF should carry a data element identifier reflecting the originator responsible for entering the transcribed data element. The source documents related to the study and from which the data elements are transcribed must be maintained and available to an FDA inspector if requested (e.g., an original or verified copy of a laboratory report; instrument printout; progress notes of the physician; the study subject's hospital chart(s), and nurses' notes). See 21 CFR 312.62(b), 312.68, 812.140(a)(3), and 812.145(b).

Other data elements, such as those originating in an electronic health record, can populate the eCRF automatically. In such situations, the electronic health record would be identified as the source of the information and must be made available for review during an FDA inspection. The sponsor and/or investigator may also be asked during the inspection to provide information on the ability of the software to transfer accurate and complete data from the electronic health record into the eCRF.[8] Algorithms for data extraction should be described in the study protocol or in another document that includes data management details. For example, some patient data in the electronic health record, such as concomitant medications, may change with time. The procedure for selecting the appropriate data element should be described.

2. Data Element Attributes and Data Element Identifiers

a. Data Element Attributes

Data element attributes are pieces of electronic information that are linked to a data element (e.g., for the data element "hemoglobin", the attributes might include the value=13gm/dl, date of the observation=February 12, 2009, observation type=laboratory test, data type=numeric), which ensure the correct electronic processing of the data element. They also provide information on the source of data elements.[9]

b. Data Element Identifiers

Data element identifiers are those attributes that identify:

[8] Ibid.

[9] See the Study Data Exchange standards on the FDA Data Standards Council Website for the technical details on data element attributes at *http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.*

- 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; and
- the study subject to which the data elements belong.

These allow FDA reviewers and investigators to examine the audit trail of the data.

c. Display of Data Element Identifiers

Although it is not necessary to automatically display the data element identifiers wherever data elements appear, the system should include a functionality that enables the user to reveal or access the data element identifiers related to each element (e.g., by cursor placement over the element, and/or a view mode displaying the data element together with its identifiers).

The following table gives examples of data elements and corresponding data element identifiers.

Table 1. -- Example of Data Elements and Data Element Identifiers*

Field in eCRF	Data Element	Data Element Identifier: Originator	Data Element Identifier: Date and Time	Data Element Identifier: Study Subject
Patient ID#	AD0012	Randomization algorithm in central computer	June 1st, 2008/3.00 pm	AD0012
Sex	male	Investigator Dr R Smith	June 1st, 2008/10.53 am	AD0012
Age	25 years	Investigator Dr R Smith	June 1st, 2008/10.53 am	AD0012
Hemoglobin	15.3 gm/dl	Co-op labs	June 2nd, 2008/noon	AD0012
**Date and time blood was drawn for hemoglobin determination	June 1st, 2008/9.23 am	Investigator Dr R Smith	June 1st, 2008/10.53 am	AD0012
Radiological report	Right upper lobe consolidation	Dr P Brown, Radiological Associates	June 1st, 2008/4.12 pm	AD0012
Blood pressure	124/88	AB instrument systems	June 1st, 2008/10.20 am	AD0012
Concomitant medications	***Lasix 40mg QD	Investigator Dr R Smith	June 1st, 2008/10.53 am	AD0012

** FDA recommends that clinical data be entered electronically by study site personnel at the time of the subject visit to avoid transcription from unnecessary paper records.*

*** The timing of certain data elements may be important (e.g., the precise time at which sample was drawn). In this case, the time that the sample was drawn should be obtained as a separate data element since the data element identifier indicates the time that the data element was entered into the computer, not the time the sample was drawn.*

**** To verify this transcribed data, FDA may request other existing documentation such as a prescription record or pharmacy record.*

3. Modifications and Corrections

Modified and/or corrected data elements should carry new data element identifiers, reflecting the date, time, and originator of the change. Both the modified data elements and their data element identifiers should be write-protected. A text field describing the reason for the change and the relationship to the original record (e.g., append, replace) should be added.

The original data element with its original data element identifiers should be preserved and available for review by FDA investigators.

The following table gives an example of a modification to a data element. This information would also apply to correcting a data element.

Table 2. – Example of Modification/Correction

Field in eCRF	Data Element	Data Element Identifier
Hemoglobin	12.3gm/dl	Modified by: Investigator assistant Dr B Green/July 7th, 2008/9.00 am/AD0012 Reason: Data error reported by Co-op labs July 6th 2008 due to standardization problem; sample was retested Original data (*write-protected automated carryover*): Hemoglobin 15.3gm/dl (Co-op labs/June 2nd, 2008/noon)/AD0012

4. Repeated Appearance of the Same Data Element in an eCRF

Occasionally a data element may appear more than once in the eCRF. A data element can automatically populate more than one appropriate location in the eCRF where it is meant to appear. However, data elements should not automatically populate multiple fields in the eCRF where the data may change. For example, a subject's weight measurement should not automatically populate later visits in the case report form since the weight may change over time.

5. Electronic Prompts to Ensure Accuracy and Completeness of Data

FDA encourages the use of electronic prompts in the eCRF to minimize errors and omissions at the time of data entry. Prompts may be designed to alert the originator to missing data, data

inconsistencies, inadmissible values, and to request additional data where appropriate (e.g., by generating an adverse event report form triggered by a critical laboratory result).

6. Originators of Data Elements

Originators of data elements can include site clinical staff entering data into a computerized system or medical devices automatically populating specific data fields in the eCRF. Examples of data originators include but are not limited to:

- Investigators or authorized study site clinical staff responsible for interviewing study subjects (The data elements they provide might be obtained either by observation of subjects or by review of patient records.)
- Biomedical devices (e.g., a blood pressure machine or EKG machine)
- Automated laboratory reporting systems
- Imaging facilities
- Consulting services (e.g., a radiologist reporting on a CT scan)
- Electronic health records programmed to populate specific data fields in the electronic case report form
- Randomization tools that assign subject numbers
- Barcode readers recording medications or devices
- Pharmacies
- Clinical study subjects (the data elements they provide might include patient reported outcomes or informed consent).

Each study site should maintain on site a list of prospectively determined originators (persons, devices, and instruments) of data elements authorized to transmit data elements to the eCRF. The list of originators should be co-developed by the sponsor and the clinical investigator. The list should include users' unique identifiers (e.g., user name) and the period for which authorization for data entry was given (see Table 3 for examples). During an inspection, this list will assist FDA's review of the audit trail for each data element. For devices and instruments, the list should include any available unique device identifier, the manufacturer, the model number, and the serial number. The list should be maintained to reflect staff changes that occur during the conduct of the clinical study.

Table 3. – Example of List of Authorized Data Originators

Category of Data Originator	List of Authorized Data Originators	Authorization Time Period
Clinical staff	Dr John M Brown	January 2, 2008-December 4 2009
	Alice Smith RN	March 5, 2008-December 12, 2009
Automated laboratory output	American Clinical Laboratories	August 30 2008-January 5, 2009
	ClinPath Services	December 21, 2007-December 12, 2009

Automated EKG machine output	Cardiology products, Model XG41, and Serial # 29834	May 13, 2008-December 12, 2009
	Cardiac monitors Inc, Model HG23, and Serial #45628	May 13, 2008-December 12, 2009
Electronic patient recorded outcome	Study subject VL0012	February 24, 2008-March 24, 2008
	Study subject VL0013	February 27, 2008- March 27, 2008
	Study subject VL0014	August 18, 2008-September 18, 2008

7. Identification of Data Originators

For those who use electronic signatures based upon the use of identification codes in combination with passwords, the clinical site must employ controls to ensure the security and integrity of the authorized user names and passwords (21 CFR 11.300(a)). Controls should:

- Confirm that the password corresponds with the identity of the user
- Confirm that the user accepts responsibility for the validity of the data entered using that password

When electronic thumbprints or other biological identifiers are used in place of an electronic password, controls should:

- Confirm that the biological identifier corresponds with identity of the user
- Confirm that the user accepts responsibility for the validity of the data entered using that biological identifier

When a device or instrument automatically populates a data field in the eCRF, a data element identifier should be created that identifies that particular device or instrument as the originator of the data element. For example, if an EKG machine automatically populates the eCRF, a data element identifying the manufacturer, model number, and serial number should be generated.

B. Tier 2 – Data Review

1. The Investigator

Investigators are those individuals who actually conduct a clinical study (i.e., under whose immediate direction the investigational product is administered or dispensed to a subject). When a study is conducted by a team of individuals, the investigator is the responsible leader of the team (21 CFR 312.3(b) and 812.3(i)). Investigators are responsible for conducting the study according to the protocol and protecting the rights, safety, and welfare of study subjects (21 CFR 312.60 and 812.100). Investigators should evaluate and act on information emerging during the course of the study. To meet this responsibility, investigators should continually assess subject

data to monitor clinical responses and to determine the need for treatment modifications. Additionally, investigators must submit certain adverse events to the sponsor (see 21 CFR 312.64(b) and 812.150(a)(1) for additional information). The investigator must also record, within each subject's case history, the observations related to the exposure of each subject to the investigational product (21 CFR 312.62(b) and 812.140(a)(3)(iii)).

To comply with the requirement to maintain accurate case histories (21 CFR 312.62(b) and 812.140(a)(3)), investigators should review completed portions of the eCRF for each subject before the data are archived and released to the parties in Tier 3 (see Fig. 1). The investigator should indicate that he/she has reviewed the submitted data. For example, an investigator might initiate an electronic command to enable transmission of data to parties in Tier 3, or append a data element identifier (with the date, time, and originator's name), indicating that the investigator has reviewed the data element. This command or appendage would be applied to all the data elements belonging to the portion of an eCRF reviewed by the investigator.

All *sub-investigators* (i.e., any member of the study team other than the clinical investigator responsible for the conduct of the study) who are involved in entering or signing off on data elements in the eCRF should be assigned their own user names and passwords.

In exceptional circumstances, the protocol may require that certain data elements be hidden from the investigator. Concurrence with this procedure should be obtained from FDA review divisions. Such data elements may be forwarded directly to parties in Tier 3 without investigator sign off.

2. The Investigator's Copy of the eCRF

The eCRF is the electronic document containing all data elements on a study subject that the investigator has reviewed prior to release to parties in Tier 3 (e.g., the sponsors, CRO, institutional review board). Portions of the eCRF may be released to parties in Tier 3 as the study progresses. The procedure and timing for release before study completion by the investigator should be included in the protocol. The eCRF should permanently carry the electronic signature of the investigator who reviewed it.

The eCRF for each subject, along with the study design and study participation data, should be stored as extensible markup language (XML) files following the current FDA Study Data Exchange Standards.[10]

The physical location of data will vary, depending on the complexity and structure of the study. For example, data reviewed and signed off by an investigator can be stored on a personal computer, a network server, an internet server, and/or a variety of storage devices (e.g., DVDs, removable drives). FDA recommends the following:

[10] See *http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm*.

- The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review and sign off.
- The clinical investigator should maintain control of these copies.
- The clinical investigator must retain a file of these copies for a minimum length of time. (See 21 CFR 312.62(c) and 812.140(d) for additional information.)
- The sponsor should describe in its standard operating procedures the location of the copies so they are available to FDA inspectors as a reference for data validation.
- Archived copies of eCRFs and other electronic documents and records required by 21 CFR 312.62(b) and 812.140(a)(3) that are pertinent to the clinical study (e.g. laboratory reports, pulmonary function test reports) should be available in read only format at the site of the study. These may be requested by FDA during a site inspection (21 CFR 312.68 and 812.145).
- 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 (see 21 CFR 312.62(c) and 812.140(d)).
- During the clinical study, archived data elements should be available in read only format to the originators who submitted them. For example, although the archived data may reside in a personal computer, a Web-based repository, a central data server, or as a paper archival copy, the laboratory should have access to the hemoglobin levels that it reports, just as the study subject should be able to review data reported in a patient-reported outcome tool or patient diary. The data that are part of the subject's case history may be requested by FDA during a site inspection (21 CFR 312.68 and 812.145).
- The investigator's copy of the eCRF should be write-protected (read only) at the time of investigator sign off. If necessary, amendments can be made separately with an appropriate audit trail, including the originator, date and time of the amendment, and reason for the amendment (see section III.A.3 of this document).

C. Tier 3 -- Data Processing and Transmission

Various available technologies can be used to acquire and transmit data electronically, provided the security of the information can be ensured and access to the system containing the data is limited to authorized password holders. Examples include traditional programs run from personal computers, Web-based systems, hand-held devices, or automatic output from laboratory instruments or medical devices.

Electronic data acquisition enables real-time transmission of data during the progress of a clinical study. For example, following investigator sign off, a sponsor may choose to automatically transmit blinded laboratory data directly into a central *safety* archive, and these data may be transmitted to a data and safety monitoring board. As part of a sponsor's designated monitoring responsibilities, a sponsor may choose to transmit study data to a CRO for real-time evaluation.

Sponsors should describe which data elements will be transmitted electronically, the origin and destination of the data elements, the parties with access to the transmitted data elements, when to transfer, and any actions, such as protocol modification, that may be triggered by real-time review of those data elements. Authorized changes to the electronic source data by the originator should be transmitted to all the data destinations. Blinding should not be compromised during the transmission of data prior to completion of the study.

IV. REGULATORY REVIEW COLLABORATION

In an effort to facilitate the review of submissions and ensure that FDA's requirements are satisfied, FDA's review divisions are available to review with sponsors their plans for the handling of electronic source data before implementation of a computerized system.

Detailed information on software development and the use of computerized systems in clinical studies can be found in FDA's guidances on the *General Principles of Software Validation* and *Computerized Systems Used in Clinical Investigations.*

Sponsors should include in their protocols information about the intended use of computerized systems during the conduct of a clinical study. Protocols should include a description of the security measures employed to protect the data in each case, and a detailed diagram and description of the transmission of electronic data.

Sponsors should also include information in the protocol about 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. Logs to record errors that are detected during the progress of a clinical study should be included.

GLOSSARY OF TERMS

The following is a list of definitions of terms used in this guidance document.

Audit Trail: A process that captures details such as additions, deletions, or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the course of such details relating to the electronic record.

Certified Copy: A copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

Computerized System: Computer hardware, software, and associated documents (e.g., user manual) that create, modify, maintain, archive, retrieve, or transmit in digital form information related to the conduct of a clinical study.

Data Element: A single observation associated with a subject in a clinical study. Examples include birth date, white blood cell count, pain severity measure, and other clinical observations made and documented during a study.

Data Element Identifier: A write-protected information tag attached to a data element that includes the origin of the data element, the date and time of entry, and the identification number of the study subject to whom the data element applies.

Data Originator: A person, device, or instrument authorized to enter the data element into the eCRF.

Direct Entry: Initial recording of data into an electronic record. Examples are the keying by an individual of original observations into a system, or automatic recording by a system of the output of a balance that measures a subject's body weight.

Electronic Record: 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 (21 CFR 11.3(b)(6)).

Electronic Signature: An *electronic signature* is computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature (21 CFR 11.3(b)(7)).

Read Only: Electronic material that can be viewed but cannot be altered or deleted.

Source Data: Also known as *original data*, those values that represent the first recording of clinical trial data elements.

Source Documents: Original documents and records including, but not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. A case report form may serve as a source document if data elements are newly created and not transcribed from other sources.

Transmit: To transfer data within or among clinical study sites, CROs, data management centers, or sponsors.

Write-Protected: Information protected by a mechanism that prevents alteration or deletion of data.