
Guidance for Industry

Electronic Source Data in Clinical Investigations

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)**

**September 2013
Procedural**

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Guidance for Industry¹

Electronic Source Data in Clinical Investigations

This guidance represents 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 guidance provides recommendations to sponsors, Contract Research Organizations (CROs), clinical investigators, and others involved in the capture, review, and retention of electronic source data in FDA-regulated clinical investigations.² In an effort to streamline and modernize clinical investigations this guidance promotes capturing source data in electronic form, and it is intended to assist in ensuring the reliability, quality, integrity, and traceability of data from electronic source to electronic regulatory submission.

This guidance addresses source data in clinical investigations used to fill the predefined fields in an electronic case report form (eCRF), according to the protocol. The guidance discusses the following topics related to electronic source data:

- Identification and specification of authorized source data originators
- Creation of data element identifiers to facilitate examination of the audit trail by sponsors, FDA, and other authorized parties
- Ways to capture source data into the eCRF using either manual or electronic methods
- Clinical investigator(s) responsibilities with respect to reviewing and retaining electronic data
- Use and description of computerized systems in clinical investigations

This guidance is intended to be used together with the FDA guidance for industry on *Computerized Systems Used in Clinical Investigations* (the computerized systems guidance),³

¹ This guidance has been prepared by 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 See definitions in 21 CFR 50.3 and 312.3.

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>; the Vaccines, Blood, and Biologics guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>; or the Medical Devices guidance Web page at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>.

and FDA regulation on Electronic Records and Electronic Signatures.⁴ Electronic structures and standards related to electronic submissions are out of scope for this guidance.

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

II. BACKGROUND

With the use of computerized systems for capturing clinical investigation data, it is common to find at least some source data recorded electronically. Common examples include, but are not limited to clinical data initially recorded in electronic health records maintained by healthcare providers and institutions, electronic laboratory reports, digital medical images from devices, and electronic diaries completed by study subjects.

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.⁵ An eCRF is an example of an electronic record.

The eCRF is an auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.⁶ Access to source data is critical to the review and inspections of clinical investigations. The review of source data by both the FDA and sponsor is important to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the clinical investigation data. Source data should be attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping.⁷ Capturing source data electronically and transmitting it to the eCRF should:

⁴ See 21 CFR part 11.

⁵ 21 CFR 11.3(b)(6).

⁶ In 21 CFR 312.62(b), reference is made to records that are part of case histories as “supporting data”; the ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance* (the ICH E6 guidance) (available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>) uses the term “source data/documents.” For the purpose of this guidance, these terms describe the same information and have been used interchangeably.

⁷ For the principal record keeping requirements for clinical investigators and sponsors developing drugs and biologics, see 21 CFR 312.50, 312.58, 312.62, and 312.68. For medical devices, see 21 CFR 812.140 and 812.145.

- Eliminate unnecessary duplication of data
- Reduce the possibility for transcription errors
- Encourage entering source data during a subject's visit, where appropriate
- Eliminate transcription of source data prior to entry into an eCRF
- Facilitate remote monitoring of data
- Promote real-time access for data review
- Facilitate the collection of accurate and complete data

III. ELECTRONIC SOURCE DATA

Electronic source data are data initially recorded in electronic format. They can include information in original records and certified copies of original records of clinical findings, observations, or other activities captured prior to or during a clinical investigation used for reconstructing and evaluating the investigation.

A. Data Capture

1. Electronic Source Data Origination

A *data element* in an eCRF represents the smallest unit of observation captured for a subject in a clinical investigation. Examples of data elements include race, white blood cell count, pain severity measurement, or other clinical observations made and documented during a study. Each data element is associated with an authorized data originator. Examples of data originators include, but are not limited to:

- Clinical investigator(s) and delegated clinical study staff
- Clinical investigation subjects or their legally authorized representatives
- Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
- Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
- Electronic health records (EHRs)
- Automated laboratory reporting systems (e.g., from central laboratories)
- Other technology

A list of all authorized data originators (i.e., persons, systems, devices, and instruments) should be developed and maintained by the sponsor and made available at each clinical site. In the case of electronic, patient-reported outcome measures, the subject (e.g., unique subject identifier) should be listed as the originator.

When identification of data originators relies on identification (log-on) codes and unique passwords, controls must be employed to ensure the security and integrity of the authorized user

names and passwords.⁸ When electronic thumbprints or other biometric identifiers are used in place of an electronic log-on/password, controls should be designed to ensure that they cannot be used by anyone other than their original owner.

When a system, device, or instrument automatically populates a data element field in the eCRF, a data element identifier (see section III.A.3) should be created that automatically identifies the particular system, device, or instrument (e.g., name and type) as the originator of the data element. For example, if an ECG machine automatically transmits to the eCRF, a data element identifier should be generated that identifies the ECG machine as the originator.

2. *Source Data Capture*

Data can be entered into the eCRF either manually or electronically as described below.

a. *Direct Entry of Data Into the eCRF*

Many data elements (e.g., blood pressure, weight, temperature, pill count, resolution of a symptom or sign) in a clinical investigation can be obtained at a study visit and can be entered directly into the eCRF by an authorized data originator. This direct entry of data can eliminate errors by not using a paper transcription step before entry into the eCRF. For these data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for FDA inspection (see section III.A.2.c).

When pertinent supportive information is available, FDA could request other documents during an inspection to corroborate a direct entry of source data elements into the eCRF by an authorized data originator. For example, at an initial visit, a clinical investigator might ask a subject about underlying illnesses, and proceed to enter the illness(es) in an eCRF. During an FDA inspection, a record may be requested for evidence of testing or the use of medications to corroborate a diagnosis.

Typically, images (e.g., CT scans) are not included as data elements in an eCRF, but rather the clinical interpretation of the image is included as a predefined data field. When an image (e.g., a CT scan) is sent to a central reading center for clinical interpretation and the radiologist is authorized to enter data directly into the eCRF, then the radiologist's assessment (e.g., *normal*) is the data element as predefined in the eCRF, the radiologist is the data originator and the CT scan is the pertinent clinical record. However, when the radiologist sends a report to a clinical investigator(s) who transcribes the data into the eCRF, the clinical investigator(s) is the originator and the source is the radiologist's report.

b. *Automatic Transmission of Data From Devices or Instruments Directly to the eCRF*

When a device or instrument is the data originator (e.g., blood pressure monitoring device or glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is the source. If a process is used by which the device or instrument transmits data automatically to, for

⁸21 CFR 11.300(a); see also the computerized systems guidance.

example, an electronic health record system or to a service provider's database, then the EHR or the service provider's database is the source.

c. Transcription of Data From Paper or Electronic Sources to the eCRF

Data elements can be transcribed into the eCRF from paper or electronic source documents. The authorized person transcribing the data from the source documents is regarded as the data originator. For these data elements, the electronic or paper documents from which the data elements are transcribed are the source. These data must be maintained by the clinical investigator(s) and available to an FDA inspector if requested (e.g., an original or certified copy of a laboratory report, instrument printout, progress notes of the physician, the study subject's hospital chart(s), nurses' notes).⁹

d. Direct Transmission of Data From the Electronic Health Record to the eCRF

Data elements originating in an EHR can be transmitted directly into the eCRF automatically. Unlike a direct transmission to an eCRF from instruments or medical devices, EHRs can use intervening processes (e.g., algorithms for the selection of the appropriate data elements). For this reason the EHR is the source, and the pertinent data for the subjects in the clinical study should be made available for review during an FDA inspection.

The ability of sponsors and/or monitors to access health records of study subjects in clinical information systems relevant to the clinical investigation should not differ from their ability to access health records recorded on paper.

e. Transmission of Data From Patient-Reported Outcome (PRO) Instruments to the eCRF

When a PRO instrument is used by a subject to transmit data elements directly to the eCRF, the subject is the data originator and the eCRF is the source. If a process is used by which the subject uses the instrument to transmit data to a technology service provider database, the service provider database is the source.

3. *Data Element Identifiers*

The eCRF should include the capability to record who entered or generated the data and when it was entered or generated. Changes to the data must not obscure the original entry, and must record who made the change, when, and why.¹⁰ Data element identifiers should be attached to each data element as it is entered or transmitted by the originator into the eCRF. Data element identifiers should contain the following:

- Originators of the data element (including those data elements entered manually (e.g., by the clinical investigator(s)) and automatically (e.g., EHR, device, or instrument))

⁹ 21 CFR 312.62(b) and 812.140(a)(3).

¹⁰ 21 CFR 11.10(e).

- Date and time the data element was entered into the eCRF (the audit trail begins at the time the data are transmitted to the eCRF)
- Clinical investigation subjects to which the data element belongs

These data element identifiers will allow sponsors, FDA, and other authorized parties to examine the audit trail of the eCRF data (and this audit trail should be readily available in a human readable form). In addition, they provide information that will allow FDA to reconstruct and evaluate the clinical investigation.

Although it is not necessary to automatically display the data element identifiers wherever data elements appear in the eCRF, the eCRF system should include a functionality that enables FDA to reveal or access the identifiers related to each data element.

4. Modifications and Corrections

Only a clinical investigator(s) or delegated clinical study staff should perform modifications or corrections to eCRF data. Modified and/or corrected data elements must have data element identifiers that reflect the date, time, originator and reason for the change, and must not obscure previous entries.¹¹ A field should be provided allowing originators to describe the reason for the change (e.g., transcription error). Automatic transmissions should have traceability and controls via the audit trail to reflect the reason for the change.

5. Use of Electronic Prompts, Flags, and Data Quality Checks in the eCRF

We encourage the use of electronic prompts, flags, and data quality checks in the eCRF to minimize errors and omissions during data entry.¹² Prompts can be designed to alert the data originator to missing data, inconsistencies, inadmissible values (e.g., date out of range), and to request additional data where appropriate (e.g., by prompting a clinical investigator(s) to complete an adverse event report form triggered by a critical laboratory result). Clinical investigator(s) should have the ability to enter comments about issues associated with the data. Sponsors should describe (e.g., in a data management plan) the electronic prompts, flags, and data quality checks that are designed to address, for example, data inconsistencies, missing data, and entries out of range.

B. Data Review

1. Clinical investigator(s)

The clinical investigator is the individual who conducts a clinical investigation (i.e., under whose immediate direction the test article or investigational product is administered or dispensed to, or used involving, a subject), or in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.¹³

¹¹ 21 CFR 11.10(e).

¹² See the computerized systems guidance.

¹³ See definitions in 21 CFR 312.3(b) and 812.3(i).

a. Clinical Investigator(s) Review and Electronic Signature

To comply with the requirement to maintain accurate case histories¹⁴ clinical investigator(s) should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to FDA.¹⁵ Use of electronic signatures must comply with part 11 (21 CFR part 11).

b. Data Exempt From Investigator Review

Under certain circumstances, the clinical investigator(s) can be masked to specific data in the eCRF. For example, in a blinded study of an osmotic diuretic, the urine osmolality should not be revealed to the clinical investigator(s). In some studies specific administrative data (e.g., code lists) might be exempt from review. Data exempt from review should be listed (e.g., in a data management plan).

2. *Modifications and Corrections During Clinical Investigator(s) Review of the eCRF*

To comply with the requirement to maintain accurate case histories,¹⁶ data elements might call for modification or correction during clinical investigator(s) review. Either the clinical investigator(s) or an originator can enter the revised data element. Modified and/or corrected data elements must have data element identifiers that reflect the date, time, originator, and reason for the change, and must not obscure previous entries.¹⁷

If changes are made to the eCRF after the clinical investigator(s) has already signed, the changes should be reviewed and electronically signed by the clinical investigator(s).

C. Retention of Records by Clinical Investigator(s)

The clinical investigator(s) should retain control of the records (i.e., completed and signed eCRF or certified copy of the eCRF). The clinical investigator(s) should provide FDA inspectors with access to the records that serve as the electronic source data.

When data elements are transcribed from paper sources into an eCRF, the clinical investigator(s) must also retain the paper sources, or certified copies, for FDA review.¹⁸ Other records (electronic and paper) required to corroborate data in the eCRF (see section III.A.2.a) may also be requested by FDA during an inspection.¹⁹

¹⁴ 21 CFR 312.62(b) and 812.140(a)(3).

¹⁵ See the ICH E6 guidance; see also 21 CFR part 11, subpart C.

¹⁶ 21 CFR 312.62(b) and 812.140(a)(3).

¹⁷ 21 CFR 11.10(e).

¹⁸ 21 CFR 312.62(b) and 812.140(a)(3).

¹⁹ Ibid.

1 **D. Data Access**

2
3 Sponsors, CROs, data safety monitoring boards, and other authorized personnel can view the
4 data elements in the eCRF before and after the clinical investigator(s) has electronically signed
5 the completed eCRF. We encourage viewing the data to allow early detection of study-related
6 problems (e.g., safety concerns, protocol deviations) and problems with conducting the study
7 (e.g., missing data, data discrepancies).
8

9 The sponsor should have a list (e.g., in a data management plan) of the individuals with
10 authorized access to the eCRF. Only those individuals who have documented training and
11 authorization should have access to the eCRF data.²⁰ Individuals with authorized access should
12 be assigned their own identification (log-on) codes and passwords.²¹ Log-on access should be
13 disabled if the individual discontinues involvement during the study.
14

15 **IV. USE AND DESCRIPTION OF COMPUTERIZED SYSTEMS IN CLINICAL**
16 **INVESTIGATIONS**

17
18 Adequate controls should be in place to ensure confidence in the reliability, quality, and integrity
19 of the electronic source data. The determination of whether a computer system used in a clinical
20 investigation is suitable for its intended purpose might not be under the control of the clinical
21 investigator(s) or sponsor (e.g., EHRs). The performance standards for these computer systems
22 may be regulated by other authorities²² and under the control of, for example, healthcare
23 providers or institutions. FDA does not intend to assess the compliance of EHRs with part 11.
24

25 Sponsors should include (e.g., in the protocol, data management plan, or investigational plan)
26 information about the intended use of computerized systems used during a clinical investigation,
27 a description of the security measures employed to protect the data, and a description or diagram
28 of the electronic data flow.
29
30
31

²⁰ See 21 CFR 11.10(i).

²¹ See 21 CFR part 11.10(d).

²² See 45 CFR part 170.

REFERENCES

Code of Federal Regulations, Title 21 part 11: Electronic Records; Electronic Signatures.

Code of Federal Regulations, Title 21 § 50.3: Definitions.

Code of Federal Regulations, Title 21 part 312: Investigational New Drug Application.

Code of Federal Regulations, Title 21 part 812: Investigational Device Exemptions.

Code of Federal Regulations, Title 45 part 170: Health Information Technology Standards, Implementation Specifications, and Certification Criteria and Certification Programs for Health Information Technology.

Food and Drug Administration, guidance for industry on *Computerized Systems Used in Clinical Investigations*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Food and Drug Administration, ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

GLOSSARY OF TERMS

The following is a list of terms and definitions used in this guidance:

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

Certified Copy: A copy (paper or electronic) 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.

Clinical Investigator: Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team (21 CFR 312.3).

Computerized System: Includes 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 investigation.

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: Information associated with 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. Once set by the computerized system, this value should not be alterable in any way.

Data Originator: Each data element is associated with an origination type that identifies the source of its capture in the eCRF. This could be a person, a computer system, a device, or an instrument that is authorized to enter, change, or transmit data elements into the eCRF (also sometimes known as an author).

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 Case Report Form (eCRF): An auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.

Electronic Health Record (EHR): An electronic record for healthcare providers to create, import, store, and use clinical information for patient care, according to nationally recognized interoperability standards. NOTE: The EHR has the following distinguishing features: able to be obtained from multiple sources, shareable, interoperable, accessible to authorized parties.

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: A 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)).

Electronic Source Data: Electronic source data are data initially recorded in electronic format.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities (in a clinical investigation) used for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Transmit: To transfer data within or among clinical study sites, contract research organizations, data management centers, sponsors, or to FDA; to transfer data, usually electronically.