Guidance for Industry

Electronic Source Data in Clinical Investigations

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

In an effort to streamline and modernize clinical investigations, this guidance provides recommendations to sponsors, Contract Research Organizations (CROs), data management centers, clinical investigators, and others involved in capturing, reviewing, and archiving electronic source data in FDA-regulated 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 electronic source data.

This guidance addresses source data from 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:

- Identifying and specifying authorized source data originators
- Creating data element identifiers to facilitate examination of the data audit trail by sponsors, FDA, and other authorized parties
- Capturing source data into the eCRF using either manual or electronic capture methods
- Investigator responsibilities with respect to reviewing and retaining electronic data

This guidance is intended to be used together with the FDA guidance for industry on *Computerized Systems Used in Clinical Investigations,*[2] and the FDA regulations on Electronic Records and Electronic Signatures (21 CFR part 11).

[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]We update and issue guidances regularly. We recommend you check the FDA Web site to ensure that you have the most up-to-date version of a guidance. FDA guidances are available on the Drugs guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; on the Vaccines, Blood, and Biologics guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm; on the Medical Devices guidance page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

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 clinical data initially recorded in electronic health records maintained by hospitals and institutions, electronic laboratory reports, electronic medical images from devices, and electronic diaries provided 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 (21 CFR 11.3(b)(6)). An electronic case report form (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 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. Access to source data is critical to the review of clinical investigations and inspection of clinical investigation sites. Both FDA's and the sponsor's review of source data are important to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the clinical investigation data. It is critical that source data be attributable, legible, contemporaneous, original, and accurately recorded (when they are acquired), and that they meet the regulatory requirements for recordkeeping.[3] Capturing source data electronically should help to:

- Eliminate unnecessary duplication of data

[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 2 years after the later 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 or a notice of completion of a product development protocol (21 CFR 812.140(d)). "A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part" (21 CFR 312.58(a)).

- Reduce the possibility for transcription errors
- Encourage entering source data during a subject's visit
- Eliminate transcribing source data before entering the data into an electronic data capture system
- Promote real-time data access for review
- Ensure the accuracy and completeness of the data

III. ELECTRONIC SOURCE DATA

Electronic source data are source data that were initially recorded electronically. 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. Source data recorded electronically, without proper controls, can be copied, transferred to other computerized systems or devices, changed, or deleted without obvious evidence of these events.

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 observation made and documented during a study.

Each data element is associated with an authorized data originator. Examples of data originators include the following:

- Investigators
- Clinical investigation site staff
- Clinical investigation subjects
- 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 (EHR)
- Automated laboratory reporting systems
- Barcode readers (e.g., that are used to record medications or devices)

For each protocol, a list of authorized data originators (i.e., persons, systems, devices, and instruments) should be co-developed and maintained by the sponsor and the investigator for each

site. The list should include unique identifiers (e.g., user name or in the case of study subjects, a unique subject identification number) and the period of time for which data originator authorization was given. The list should be maintained to reflect staff changes that occur during the conduct of the investigation.

The list should identify the systems, devices, and instruments that transmit data elements directly into the eCRF. In the case of electronic patient diaries, the subject should be listed as the originator.

When identification of data originators relies on log-on codes and passwords, controls must be employed to ensure the security and integrity of the authorized user names and passwords (21 CFR 11.300(a)). 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 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 may eliminate errors by not using a paper transcription step before entry into the eCRF. For these data elements, the eCRF is the source.

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.

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

When a medical device or instrument (e.g., glucometer, blood pressure monitoring device, or electronic patient diary) automatically transmits data elements directly to the eCRF without any intervening process, the eCRF is the source. When an intervening process (e.g., ECG device transmission to a central reading center) is used, the source may be the device or central reading center. The intervening process and data flow should be described (e.g., in the data management plan).

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 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), and nurses' notes) (21 CFR 312.62(b), 812.140(a)(3)).

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 may use intervening processes (e.g., algorithms for the selection of the appropriate data elements). For this reason the EHR is the source and should be made available for review during an FDA inspection.

We recognize that sponsors rarely have control of EHRs at clinical investigational sites. The ability of sponsors and/or monitors to access health records in clinical information systems should not differ from their ability to access health records recorded on paper.

3. Data Element Identifiers

Data element identifiers are computer-generated metadata tags that 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 investigator) and automatically (e.g., EHR, device, or instrument))
- Date and time that the data element was entered into the eCRF
- Study subject 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 data. 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, the eCRF system should include a functionality that enables the reviewer to reveal or access the data element identifiers related to each data element.

4. Modifications and Corrections

Modified and/or corrected data elements should have new data element identifiers, reflecting the date, time, and originator of the change. These modified and/or corrected data elements should not obscure previous entries. A field should be provided allowing originators to describe the reason for the change and the relationship to the original record (e.g., append, replace).

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. 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 an investigator to complete an adverse event report form triggered by a critical laboratory result).

B. Data Review

1. Investigator

The investigator is the individual who actually 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 (21 CFR 312.3(b), 21CFR 812.3(i))).

a. Investigator Review and Electronic Signature

To comply with the requirement to maintain accurate case histories (21 CFR 312.62(b) and 812.140(a)(3)), investigators should review and electronically sign the eCRF for each subject before the data are archived or submitted to FDA.[4] The following should be performed:

- Periodic review and electronic signing of the eCRF by the investigator during the conduct of the clinical investigation and evidence of this review should be contained in the audit trail.

- Tag the data element with computer-generated metadata (data element identifiers) that are included in the portions of the eCRF that have been signed by the investigator, indicating when the investigator sign-off was performed (date and time) and by whom.

- When the investigator is responsible for both entering data elements (data originator) and for signing the eCRF, reflect in the metadata the investigator as both the originator and the person responsible for sign-off.

[4] International Conference on Harmonization (ICH) guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*, available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

b. Data Elements Exempt from Investigator Review

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

2. Modifications and Corrections During Investigator Review

During investigator review, data elements might require modification or correction. Either the investigator or the originator can enter the revised data element. Modified and/or corrected data elements should have new data element identifiers, reflecting the date, time, and originator of the change. These modified and/or corrected data elements should not obscure previous entries. A field should be provided allowing originators to describe the reason for the change and the relationship to the original record (e.g., append, replace).

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

3. Review and Sign-Off by Other Members of the Study Team

Any member of the study team responsible for entering or signing-off on data elements in the eCRF should be assigned his/her own log-on codes and passwords. Log-on access should be disabled if the member discontinues involvement in the study and is no longer an authorized data originator. In addition, the investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.[5]

C. Retention of Records by Investigator

Access to a signed electronic copy of the eCRF should be controlled by the investigator and made available upon request during a site inspection. When data elements are transcribed from paper sources into an eCRF, the investigator must also retain the paper sources, or certified copies, for FDA review (see 21 CFR 312.62(b) and 812.140(a)). Other records (electronic and paper) required by 21 CFR 312.62(b) and 812.140(a)(3) to corroborate data in the eCRF (see section III.A.2.a) may also be requested by FDA during a site inspection.

D. Data Access

Sponsors, CROs, data safety monitoring boards, and other authorized personnel can view the data elements in the eCRF before the investigator has signed-off. We encourage viewing the data to allow early detection of study-related problems (e.g., safety concerns, protocol violations) and problems with conducting the study (e.g., missing data, data discrepancies**)**. Any interim analyses based on ongoing electronic review should be pre-specified in the protocol.

[5] Ibid., p. 14.

The sponsor should have a list of the individuals with authorized access, by privilege level, who can view the data electronically (e.g., in the data management plan).

IV. DESCRIPTION AND USE OF ELECTRONIC CASE REPORT FORM

Sponsors should include (e.g., in the data management plan) information about the intended use of computerized systems used during a clinical investigation. A description of the security measures employed to protect the data and a description of the flow of electronic data should be prepared.

Sponsors should also include information on electronic prompts, flags, and data quality checks in the eCRF that are designed to address, for example, data inconsistencies, missing data, and entries out of range.

Sponsors should ensure that clinical investigators and study site staff are adequately trained to use the eCRF appropriately.

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 *certified copy* is 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: A *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: An information tag or metadata 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 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 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: An *electronic signature* is 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: Source data (see below) that was initially recorded electronically.

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.