Electronic Source Data in Clinical Investigations – FDA Guidance

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FDA recently released guidance for industry entitled,Electronic Source Data in Clinical Investigations (September 2013) (Guidance). Building on the November 2012 draft guidance, this final Guidance addresses source data that is used to fill in predefined fields in electronic case report forms (eCRFs) in FDA-regulated clinical investigations.

Most clinical investigations involve at least one of the following: eCRFs, electronic health records (EHRs) and/or other forms of electronic data or databases. The Guidance is relevant for trial sponsors, investigators, institutions, CROs, core labs and others involved in the collection and review of electronic data for clinical trials. Care should be taken to review the Guidance, as it sets forth regulatory recommendations (guidances are not binding but rather reflect FDA's current thinking) and contains important terminology and practical examples of electronic and other source data and data flow into the eCRF.

This Update highlights features of the Guidance

Source Data

The Guidance "promotes capturing source data in electronic form." Further, it is "intended to assist in ensuring the reliability, quality, integrity, and traceability of data from electronic source to electronic regulatory submission."

According to the Guidance, the review of source data by both FDA and the sponsor is important for human subject protection and trial quality and integrity purposes. Further, source data should be "attributable, legible, contemporaneous, original, and accurate (ALCOA) and must meet the requirements for recordkeeping."

Data Elements and Identifiers

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The Guidance presents mechanics for electronic data capture. The smallest unit of observation for a trial subject is the "data element." Each data element should be associated with an authorized "data originator." Data originators include investigators, subjects, consulting services, medical devices, EHRs, automated lab reporting systems and other technology.

Data contained in eCRFs must have "data element identifiers." These identifiers should include the originator of the data element, date and time the element was entered into the eCRF, and the trial subject. If the investigator or delegated staff modifies any eCRF data, the modified data elements must have data element identifiers that indicate the originator, time and date, and reason for the modification, and must not obscure earlier entries.

The data element identifiers do not need to appear when a data element is displayed in the eCRF but should be available for review by FDA, sponsors and other authorized parties to examine the audit trail of the eCRF data. For eCRFS that are automatically populated, a data element identifier should automatically identify the applicable system, device or instrument as the originator of the data element.

Source Data Access and EHRs

The Guidance describes various forms of manual and electronic source data capture for eCRFs. It makes clear that both FDA and sponsors must be given access to the site's source data – paper and electronic and whether or not part of an EHR system – for inspection and review.

Further, sponsors, CROs, DSMBs and other authorized personnel should have the ability to review the data elements in the eCRF both before and after the investigator has electronically signed the eCRF.

As trial sites' use of EHRs grows increasingly common, many sponsors find the process of ensuring source data verification at the sites challenging, as sites often do not want to provide monitors with access to the sites' EHRs for source data verification purposes. With this new guidance, sponsors now have more definitive regulatory language to support this request. The guidance states, "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… 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."

As in the past, sponsors must take care to ensure that the subject HIPAA authorizations provide the sponsor adequate rights to access source data that contain protected health information, even if that data is in the EHR system.

Notably, the Guidance states, "FDA does not intend to assess the compliance of EHRs with Part 11." However, the guidance states that "adequate controls should be in place to ensure confidence in the reliability, quality, and integrity of the electronic source data."

Certain Sponsor Obligations

Among the steps that sponsors should take, the Guidance states the following:

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The sponsor's protocol or data management plan should include :

1. information about the intended use of computerized systems in the trial;
2. description of security measures used to protect the data; and
3. description or diagram of the electronic data flow.

The sponsor should have a list, such as in the data management plan, of the individuals who are authorized to access the eCRF.

The sponsor should describe, such as in the data management plan, "the electronic flags, prompts and data quality checks that are designed to address, for example, data inconsistencies, missing data, and entries out of range."

The sponsor must develop and maintain "a list of all authorized data originators (i.e., persons, systems, devices, and instruments)." The sponsor should make this list available at each trial site.

Sponsors should review their protocols, data management plans and documentation at the sites for compliance with this latest guidance.

Part 11 Regulations, Guidance and Enforcement Discretion

The use of electronic records in connection with clinical trials is regulated under 21 CFR Part 11 (Part 11). Part 11 was issued in March 1997 and sets forth criteria for acceptance by FDA

of electronic records, electronic signatures and handwritten signatures executed to electronic records (in lieu of handwritten signatures executed on paper). Part 11 and the associated guidances have had a somewhat tortuous journey, and the Guidance makes real strides in setting forth clearer obligations.

With the advent of this latest Guidance, three main FDA guidances now apply to records regulated by Part 11: the Guidance discussed here, the May 2007 FDA guidance for industry on Computerized Systems Used in Clinical Investigations (Computerized Systems Guidance) and the August 2003 FDA guidance for industry on Part 11, Electronic Records; Electronic Signatures – Scope and Application (Scope and Application Guidance). The remainder of this section discusses FDA's intent to exercise enforcement discretion with regard to certain requirements of Part 11.

After its release, Part 11 quickly became viewed as impenetrable. FDA responded by announcing, in the Scope and Application Guidance, its intent to reexamine Part 11 and to exercise enforcement discretion with regard to Part 11 requirements for validation, audit trails, record retention and record copying.

The new Guidance states that it is meant to be used in conjunction with Part 11 and the Computerized Systems Guidance. The Computerized Systems Guidance states that it supplements the Scope and Application Guidance, and both of these earlier guidances discuss FDA's intent to exercise enforcement discretion with regard to the Part 11 requirements noted above.

In contrast to the two earlier guidances, the Guidance is silent on the issue of enforcement discretion. Further, the Guidance imposes obligations that are strikingly similar to portions of the Part 11 requirements that are the subject of FDA's enforcement discretion, such as audit trails. In light of this most recent guidance, trial sponsors should proceed with caution before disregarding sections of Part 11 that have been designated for enforcement discretion and should do so

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only after careful consideration of all relevant factors.

If you have any questions or would like more information about these developing issues, please contact the following:

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