JOURNAL OF CLINICAL RESEARCH BEST PRACTICES
Vol. 12, No. 7, July 2016 "Happy Trials to You"

What's New in GCP? EHRs Used in Trials Don't Have to be Part 11 Compliant, but Still Must be Valid

While the FDA "does not intend to assess compliance" of electronic health records (EHRs) used in clinical investigations with 21 C.F.R. Part 11, "FDA's acceptance of data from clinical investigations for decision-making purposes depends on FDA's ability to verify the quality and the integrity of data during FDA on-site inspections and audits. Sponsors are responsible for assessing the validity, reliability and integrity of any data used to support a marketing application for a medical product."

The FDA clarified its expectations for EHRs used as source data in clinical investigations in draft guidance issued May 16.

The guidance added that "if the data elements obtained for the sole purpose of a clinical investigation are entered directly into the EHR by study personnel, the individual entering the study-specific data should be identified as the originator." In addition, the "FDA intends to assess compliance with 21 C.F.R. Part 11…on data derived from the EHR at the point when that data enter the sponsor's electronic system supporting the clinical investigation. For purposes of data traceability, the originator of the data elements should be identified along with an electronic date and time stamp at the time data enter the sponsor's electronic system."

The guidance provides recommendations on:

- deciding whether and how to use EHRs as a source of data in clinical investigations;
- using EHRs that are interoperable with electronic systems supporting clinical investigations;
- ensuring the quality and the integrity of EHR data that are collected and used as electronic source data in clinical investigations; and
- ensuring that the use of EHR data collected and used as electronic source data in clinical investigations meets FDA's inspection, recordkeeping and record retention requirements.

The FDA said the draft guidance recommendations "apply to the use of EHR data in prospective clinical investigations of human drugs and biological products, medical devices, and combination products. This includes foreign clinical studies not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE) that are submitted to FDA in support of an application for the marketing approval of a medical product" (see 21 C.F.R.§314.106, 21 C.F.R. §312.120 and 21 C.F.R. §814.15).

However, the guidance does not apply to the use of EHR data in post marketing observational pharmacoepidemiologic studies designed to assess the risk associated with a drug exposure or designed to test pre-specified hypotheses for such studies, or when EHR data are used as a recruitment tool for clinical investigations.

The FDA noted that "in general, EHRs are not under the control of FDA-regulated entities" because in most instances, these systems belong to health care organizations and institutions. The "FDA encourages sponsors and clinical investigators to work with the entities that control the EHRs" to use EHRs and electronic data capture (EDC) systems that are interoperable. "Interoperable technology may involve automated electronic transmission of relevant EHR data to the EDC system."

The guidance added "Interoperable technology may also allow full integration of the EDC system with the EHR so that the clinical investigator and the patient's other health care

providers would have access to all of the research and clinical care data as appropriate." However, "such access must be described in the informed consent," the guidance cautioned.

"Full integration of both systems may reduce the use of stand-alone EDC systems by health care providers who are participating as investigators in clinical investigations," the draft guidance said. "In addition, an interoperable EHR-EDC system could provide the ability to integrate with other health care clinical information systems," such as radiology and laboratory services.

ONC Certified EHR Technology Encouraged

The guidance noted the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH Act) directed the Office of the National Coordinator for Health Information Technology (ONC) to establish a voluntary certification program for health information technology. "Use of such certified EHR technology is encouraged and, if used, would give FDA confidence during inspections that the EHR data is reliable and that the technical and software components of privacy and security protection requirements have been met," the guidance said.

However, if the EHRs are not certified by ONC, they can still "provide adequate data to inform FDA's regulatory decisions, provided that adequate controls are in place to ensure the confidentiality, integrity and reliability of data."

Sponsors should consider whether EHRs not certified by ONC "have adequate controls in place to ensure that the confidentiality, integrity and reliability of data are preserved," the guidance said. Sponsors should consider whether the system has the following internal security safeguards:

- access to electronic systems is limited to authorized users;
- authors of records are identifiable;
- audit trails are available to track changes to data;
- and records are available and retained for FDA inspection for as long as the records are required by applicable regulations.

If the clinical investigation site is using a system that does not contain the adequate controls, "sponsors should consider the risks of employing such systems (e.g., the potential harm to research subjects, patient privacy rights, and data integrity of the clinical investigation and its regulatory implications)," the guidance said.

The FDA noted the use of EHRs as a source of data in clinical studies "may require some additional considerations, planning and management. Therefore, sponsors should include (e.g., in the protocol or the data management plan) information about the intended use of the EHR during a clinical investigation and a description or diagram of the electronic data flow between the EHR and the sponsor's electronic system supporting the clinical investigation," including a description of how the relevant EHR data are extracted and subsequently imported into the sponsor's electronic system.

Sponsors also should check the extracted data for consistency and completeness with the source data obtained from the EHR, and make corrections when errors are found to properly align the source data with the extracted data. In addition, sponsors should ensure that data obtained from the EHRs are consistent with the data collection specified in the clinical protocol.

Sponsors also should ensure that software updates to the sponsor's electronic system or the EHR do not affect the reliability and the integrity of EHR data entering the sponsor's electronic system, and they should consider the clinical investigator's ability to appropriately

archive and backup any EHR data that may be used for the clinical study so that data are not lost before the record retention period.

Sponsors also should ensure that study monitors have suitable access to all relevant subject information pertaining to a clinical investigation, as appropriate. The guidance noted the monitor access "must be described in the informed consent (21 C.F.R. §50.25(a)(2))."

The guidance also noted that "sponsors should discuss with the relevant FDA review division any unique issues or challenges encountered that are related to the data collection from the EHRs."

When health care professionals who are not part of the clinical investigation make modifications or corrections to data in the EHR that will be used for the clinical investigation, "it is important to ensure that these modifications are made without obscuring previous entries," the guidance said. "The sponsor's electronic system should capture any updated information as well as any accompanying audit trail information."

Sponsors and clinical investigators must ensure that there are adequate methods to monitor, track and document all changes made to information in the EHR pertaining to the conduct of the trial. "The audit trail documentation of the EHR should be retained for a time period that is at least as long as the time period required for the subject's electronic records and should be available for FDA to review and copy," the guidance said (21 C.F.R. §312.58, 21 C.F.R. §312.68, and 21 C.F.R. §812.145).

Informed Consent Concerns Detailed

"The informed consent for clinical investigations in which EHRs will be used must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and must also identify all entities who may gain access to the patient's electronic health record relating to the clinical investigation (21 C.F.R. §50.25(a)(5)). The extent of access to EHRs granted to other parties, such as sponsors, contract research organizations, and study monitors, must also be described (21 C.F.R. §50.25(a) (5))," the guidance said.

Sponsors also should consider "whether there are any reasonably foreseeable risks with the use of EHRs," such as an increased risk of data breaches, which must be described to the subject in the informed consent (21 C.F.R. §50.25(a)(2)).

"For systems that are interoperable, to allow for a clear description of the parties granted access to the patient's data in the informed consent, sponsors and clinical investigators should have a detailed understanding of data flow and data visibility," the guidance added.

Sponsors also need to consider "the safeguards that are in place to ensure the privacy and confidentiality of data from subjects who participate, who decide to discontinue participation in a clinical investigation, who are withdrawn by their legally authorized representative, as applicable, or who are discontinued from participation by the clinical investigator," the guidance said. In addition, "clinical investigators should comply with any privacy and security requirements applicable to their institution or organization."

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