

What's New in GCP? FDA Issues Guidance on Use of Electronic Health Records in Trials

Although the FDA does not intend to assess electronic health record (EHR) systems that provide data for clinical trials for compliance with 21 C.F.R. Part 11, sponsors' electronic data capture (EDC) systems that extract EHR data for use in clinical investigations will have to follow Part 11, according to FDA guidance released July 18.

However, even though the EHR systems do not have to be Part 11 compliant, the FDA's "acceptance of data from clinical investigations for decision-making purposes depends on FDA's ability to verify the quality and integrity of the data during FDA inspections."

The guidance on the use of electronic health record data in clinical investigations "facilitates the use of electronic health record data in clinical investigations and helps integrate data collected in routine care settings into clinical trials," said Jacqueline Corrigan-Curay, director of the Center for Drug Evaluation and Research's Office of Medical Policy, in announcing the new guidance. "Harnessing the real-world data being captured in electronic health records enables clinical investigators to collect data from routine medical care and generate scientific evidence that's appropriate for regulatory decision making. It also helps generate accurate, science-based information that health care professionals and patients need to use medical products to maintain and improve public health," Corrigan-Curay said.

The guidance provides recommendations on:

- Deciding whether and how to use EHRs as a source of data in clinical investigations;
- Using EHR systems that are interoperable with EDC systems in clinical investigations;
- Ensuring the quality and integrity of EHR data 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 (21 C.F.R. § 312.62, 21 C.F.R. § 312.68, 21 C.F.R. § 812.140 and 21 C.F.R. § 812.145).

The FDA noted the guidance applies to data obtained from EHRs and EHR clinical data warehouses.

However, the guidance does not apply to:

- The use of EHR data in postmarketing observational pharmacoepidemiologic studies designed to assess adverse events and risks associated with drug exposure or designed to test prespecified hypotheses for such studies;
- The use of EHR data to evaluate feasibility of the trial design or as a recruitment tool for clinical investigations; or
- Data collected for registries and natural history studies.

The guidance encourages sponsors and clinical investigators to work with entities that control EHR systems, such as health care organizations, to use EHR and EDC systems that are interoperable or fully integrated. The FDA noted noninteroperable systems involve manual transcription of data elements from the EHR to the eCRF or to the paper case report form. "Such manual transcription procedures may introduce risks of data entry errors unless effective quality control systems are in place," the guidance said.

In addition, “diverse ownership of electronic systems and data may necessitate appropriate collaboration between the health care and clinical research communities. FDA encourages sponsors and health care organizations to work with EHR and EDC system vendors to further advance the interoperability and integration of these systems.”

Exchange Structured Data

The guidance also encourages the exchange of structured data (e.g., demographics, vital signs, laboratory data) between EHR and EDC systems so that data may be entered once at the point-of-care and used many times without manual re-entry or manual source data verification.

“Sponsors should ensure that the structured data elements obtained from the EHR correspond with the protocol-defined data collection plan (e.g., time and method of measurement). In addition, for extraction of unstructured data, sponsors should consider the reliability and quality of unstructured EHR data and the appropriateness of using it as critical source data, such as study endpoints,” the guidance said.

Sponsors also “should ensure that the interoperability of EHR and EDC systems (e.g., involving the automated electronic transmission of relevant EHR data to the EDC system) functions in the manner intended in a consistent and repeatable fashion and that the data are transmitted accurately, consistently and completely. The sponsor’s quality management plan (e.g., standard operating procedures, software development life cycle model, change control procedures) should address the interoperability of the EHR and EDC system and the automated electronic transmission of EHR data elements to the EDC system,” the guidance said.

As well, sponsors should ensure that software updates to their EDC systems do not affect the integrity and security of EHR data transmitted to the system. In addition, as part of the quality management plan, the FDA “encourages sponsors to periodically check a subset of the extracted data for accuracy, consistency, and completeness with the EHR source data, and make appropriate changes to the interoperable system when problems with the automated data transfer are identified,” the guidance said.

In cases where data from multiple EHR systems from different health care organizations and institutions are integrated with EHR data at the clinical investigation site, data from another institution’s EHR system may be used and transmitted to the sponsor’s EDC system, provided that data sharing agreements are in place.

Sponsors and clinical investigators also should ensure that policies and processes for the use of EHRs at the clinical investigation site are in place and that there are appropriate security measures employed to protect the confidentiality and integrity of the study data. Sponsors should also ensure that study monitors have suitable access to all relevant subject information pertaining to a clinical investigation, as appropriate.

Consent Must Discuss Access to EHR

Such access must be described in the informed consent (21 C.F.R. § 50.25(a)(5)). The consent must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (21 C.F.R. § 50.25(a)(5)) and should identify entities, such as health care providers, clinical investigators, sponsors, contract research organizations, study monitors, and regulatory agencies that may gain access to the patient’s EHR relating to the clinical investigation.

In addition, the consent process must note the possibility that FDA may inspect records (21 C.F.R. § 50.25(a)(5)) and should not state or imply that FDA needs permission from the subject for access to the records. The consent also should not promise or imply absolute confidentiality by the FDA.

The FDA also noted that the HHS Office of the National Coordinator for Health Information Technology (ONC) has established a voluntary ONC Health IT Certification Program. "FDA encourages the use of such certified EHR systems together with appropriate policies and procedures for their use," the guidance said.

Sponsors should include in their data management plan a list of EHR systems used by each clinical investigation site in the clinical investigation. Sponsors should document the manufacturer, model number, and version number of the EHR system and whether the EHR system is certified by ONC.

In addition, if an EHR system is decertified during a clinical investigation because the system no longer conforms to ONC's certification criteria, "sponsors should determine the nature or reasons for the nonconformity and determine whether it would affect the quality and integrity of data used in the clinical investigation," the FDA said.

The guidance added that EHR systems not certified by ONC, including EHR systems at foreign clinical sites, "can provide adequate data to inform FDA's regulatory decisions, provided that adequate controls are in place to ensure the confidentiality, integrity and security of data. "For systems not certified by ONC, sponsors should consider whether the systems have controls in place to ensure that the confidentiality, integrity and security of data are preserved, such as:

- policies and processes for the use of EHR systems at the clinical investigation site are in place;
- appropriate security measures are employed to protect the study data;
- 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.

Record Retention Still Required

For human drugs and biological products, clinical investigators must retain all records, including case histories and other EHR data pertaining to a clinical investigation, as required by 21 C.F.R. Part 312, for 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.

For medical devices, an investigator or sponsor must maintain all records, including EHRs relating to the investigation, as required by 21 C.F.R. § 812.140(d), during the investigation and for two years after the latter of two dates: the date on which the investigation is terminated or completed and the date that the records are no longer required for the purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

The guidance noted that 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).”

Sponsors also should consider EHR system certification information from other authorizing bodies outside the United States, including information about aspects of the EHR system that the authorizing body evaluated when certifying the EHR system, and feature and product-specification information from the EHR system.

In addition, for the purposes of recordkeeping, audit trails, and inspection, each electronic data element should be associated with a data originator. “Identifying the EHR as the data originator may be sufficient because sponsors are not expected to know details about all users who contribute information to the patient’s HER,” the guidance said.

“After data are transmitted to the eCRF, the clinical investigator or delegated study personnel should be the only individuals authorized to make modifications or corrections to the data,” the guidance said. “Modified and corrected data elements should have data element identifiers that reflect the date, time, data originator, and the reason for the change. Modified and corrected data should not obscure previous entries.”

In addition, clinical investigators should review and electronically sign the completed eCRF for each study participant before data are archived or submitted to the FDA. If modifications are made to the eCRF after the clinical investigator has signed the eCRF, the changes should be reviewed and approved by the clinical investigator.

When a study design is blinded, “sponsors should consider whether the use of interoperable EHR and EDC systems has any potential to unblind the treatment allocation,” the guidance said. “If a potential for unblinding is identified, sponsors should determine whether the use of interoperable systems is appropriate or whether other appropriate controls should be in place to prevent unblinding.”

The guidance also advised that, at any time during clinical investigation, “sponsors should discuss with the relevant FDA review division any unique issues or challenges encountered relating to the data collection from the EHRs.”

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