Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

DRAFT GUIDANCE

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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)

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TABLE OF CONTENTS

Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors, clinical investigators, contract research organizations, institutional review boards (IRBs), and other interested parties on the use of electronic health record (EHR) data in FDA-regulated clinical investigations.[2] For the purposes of this guidance, EHRs are electronic platforms that contain individual electronic health records for patients and are maintained by health care organizations and institutions. For example, a typical EHR may include a patient's medical history, diagnoses, treatment plans, immunization dates, allergies, radiology images, pharmacy records, and laboratory and test results. EHRs can be used by health care institutions to integrate real-time electronic health care information from medical devices and different health care providers involved in the care of patients. This guidance uses a broad definition for EHRs in an attempt to be inclusive of many different types of EHRs.

This 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[3] supporting clinical investigations
- Ensuring the quality and the integrity of EHR data that are collected and used as electronic source data[4] in clinical investigations

[1] This guidance has been prepared by the Office of Medical Policy and the Office of Translational Sciences in the Center for Drug Evaluation and Research (CDER) in coordination with the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration. This guidance was developed in consultation with the Department of Health and Human Services' (HHS) Office of the National Coordinator for Health Information Technology (ONC).

[2] For FDA's regulatory definitions of clinical investigation, see 21 CFR 50.3(c), 56.102(c), and 312.3(b). For FDA's regulatory definition of an investigation, see 812.3(h).

[3] For the purposes of this guidance, *electronic systems* are systems that produce electronic records.

[4] *Electronic source data* refer to data initially recorded in electronic format.

- 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[5]

In an effort to modernize and streamline clinical investigations, the goals of this guidance are as follows:

- Facilitate the use of EHR data in clinical investigations
- Promote the interoperability of EHRs and electronic systems supporting the clinical investigation

This guidance expands upon recommendations found in the following guidances for industry[6] as they relate to electronic source data from EHRs that are owned and managed by health care organizations:

- *Computerized Systems Used in Clinical Investigations*
- *Electronic Source Data in Clinical Investigations*

In general, FDA's guidance documents 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. SCOPE

The recommendations outlined in this guidance apply to the use of EHR data in prospective clinical investigations of human drugs and biological products,[7] 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 CFR 314.106, 312.120 and 814.15).

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[5] For inspection and principal recordkeeping requirements for sponsors and clinical investigators who develop human drugs and biological products, see 21 CFR 312.57, 312.58, 312.62, and 312.68. For medical devices, see 21 CFR 812.140 and 812.145.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance Web page. CDER guidance documents are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; CBER guidance documents are available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm; and CDRH guidance documents are available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

[7] For the purposes of this guidance, all references to *medical products* include human drugs and biological products, medical devices, and combination products that are regulated by CDER, CBER, or CDRH.

This guidance does not apply to the use of EHR data:

- In postmarketing observational pharmacoepidemiologic studies designed to assess the risk associated with a drug exposure or designed to test prespecified hypotheses for such studies[8]

- When used as a recruitment tool for clinical investigations[9]

III. BACKGROUND

FDA issued guidance on electronic source data in clinical investigations (eSource guidance).[10] In the eSource guidance, FDA addresses attributes of source data[11] used to fill predefined fields in an electronic case report form (eCRF)[12] that would satisfy FDA's inspection, recordkeeping, and record retention requirements.[13] The guidance acknowledges that data entering the sponsor's eCRF may be derived from a variety of sources, including EHRs.

In general, EHRs are not under the control of FDA-regulated entities (e.g., sponsors, clinical investigators), because in most instances, these systems belong to health care organizations and institutions. As provided in the eSource guidance, FDA does not intend to assess compliance of EHRs with 21 CFR part 11.[14] However, 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 (see 21 CFR parts 312 and 812). Sponsors are responsible for assessing the validity, reliability, and integrity of any data used to support a marketing application for a medical product. Therefore, this guidance clarifies FDA's expectations when EHRs are used as a source of data in clinical investigations.

Potential Advantages of EHRs

With the widespread use of EHRs, there are opportunities to improve patient safety, data accuracy, and clinical trial efficiency when data from these systems are used in clinical

[8] When using EHR data for postmarketing observational pharmacoepidemiologic studies designed to assess the risk associated with a drug exposure, sponsors should follow the recommendations in the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

[9] For more information, see FDA's information sheet guidance for institutional review boards and clinical investigators *Recruiting Study Subjects.*

[10] See FDA's guidance for industry *Electronic Source Data in Clinical Investigations.*

[11] *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 the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

[12] An *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.

[13] See footnote 5.

[14] See footnote 10.

investigations. EHRs may enable clinical investigators and study personnel to more easily combine, aggregate, and analyze data from many different sources (e.g., clinical notes; physician orders; and radiology, laboratory and pharmacy records). EHRs may have the potential to provide clinical investigators and study personnel access to real-time and longitudinal health care data for review and can facilitate post-trial follow-up on patients to assess long-term safety and efficacy of medical products. There are also opportunities for long-term follow-up of large numbers of patients in studies where primary endpoints are rare, such as in prophylaxis studies.

IV. INTEROPERABILITY

For the purposes of this guidance, *interoperability* refers to the ability of two or more systems or components to exchange information and to use the information that has been exchanged. The interoperability and automated electronic exchange of information between the EHR and the sponsor's electronic system supporting the clinical investigation, such as an electronic data capture (EDC) system,[15] may benefit the clinical investigation and patients and other health care providers. The interoperability between EHRs and EDC systems may simplify data collection for a clinical investigation by enabling clinical investigators and study personnel to capture source data at the time of a subject's point-of-care visit. These interoperable systems may reduce errors in data transcription and provide data that is more accurate and complete allowing for improvement in the quality of clinical investigations and the interpretation of data. Interoperability offers the opportunity for health care professionals who are not part of the clinical investigation to be aware of and treat emerging health care issues that arise as a part of the clinical investigation and document such issues in the EHR.

FDA encourages sponsors and clinical investigators to work with the entities that control the EHRs, such as health care organizations, to use EHRs and EDC systems that are interoperable. EHRs may be interoperable with EDC systems in a variety of ways depending on supportive technologies and standards. Interoperable technology may involve automated electronic transmission of relevant EHR data to the EDC system. For example, data elements originating in an EHR (e.g., demographics, vital signs, past medical history, past surgical history, social history, medications, adverse reactions) may automatically populate the eCRFs within an EDC system.

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. Such access must be described in the informed consent (see 21 CFR 50.25(a)(5)) (see section VI.D of this guidance). 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. In addition, an interoperable EHR-EDC system could provide the ability to integrate with other health care clinical information systems (e.g., radiology information systems, laboratory information systems).

[15] *EDC systems* refer to electronic systems designed to collect and manage clinical trials and laboratory data in an electronic format. One type of an EDC system is an eCRF.

In contrast, noninteroperable technology, without the capability for direct exchange of EHR data in clinical investigations, may involve manual transcription of data elements from the EHR to the eCRF or to the paper case report form, similar to the transcription performed with paper records.

There can be many practical challenges to the interoperability of EHRs and EDC systems. These challenges may include the complex and diverse clinical data standards used by the health care and clinical research communities, which may hinder the exchange of information between different electronic systems. Also, diverse ownership of electronic systems and data can necessitate appropriate collaboration between the health care and clinical research communities. Many of these challenges are being addressed by the adoption of data standards as well as through standardization requirements as part of the ONC Health Information Technology (Health IT) Certification Program.[16]

In general, the EHR is identified as the originator of the data elements that are obtained for a clinical investigation in the course of routine clinical care.[17] However, if the data elements obtained for the sole purpose of a clinical investigation are entered directly into the EHR by study personnel (e.g., by using a dedicated research module within the EHR), the individual entering the study-specific data should be identified as the originator. In general, FDA intends to assess compliance with 21 CFR part 11 as provided in the guidance for industry *Part 11, Electronic Records; Electronic Signatures – Scope and Application*[18] on data derived from the EHR at the point when that data enter the sponsor's electronic system supporting the clinical investigation. For the purposes of data traceability, the originator of the data elements[19] (i.e., EHR or study personnel entering or modifying the clinical study data) should be identified along with an electronic date and time stamp at the time data enter the sponsor's electronic system.[20] In such cases, the sponsor should ensure that the appropriate authority controls are in place to limit system access for entering and modifying data to the research component of the EHR to study personnel only.

V. BEST PRACTICES FOR THE USE OF EHR DATA IN CLINICAL INVESTIGATIONS

When EHRs are used as a source of data in clinical investigations, sponsors should ensure that the EHRs they use and the processes and policies for their use provide electronic source data that are attributable, legible, contemporaneous, original, and accurate (ALCOA).[21] FDA considers the fundamental elements of data quality to be ALCOA.

[16] ONC certification program and processes are discussed further in section V.A of this guidance.
[17] See footnote 10.
[18] For more information, see guidance for industry *Part 11, Electronic Records; Electronic Signatures – Scope and Application*.
[19] *Data element* is 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.
[20] See footnote 10.
[21] For more information, see FDA's guidance for industry *Computerized Systems Used in Clinical Investigations*.

A. Use of ONC-Certified Health Information Technology

The Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH Act) requires that ONC establish a voluntary certification program for health IT.[22] ONC has adopted use of the broader term *health IT* in the ONC Health IT Certification Program that includes EHRs and other forms of health information technology that provides electronic data.[23]

Under the ONC Health IT Certification Program, certified EHR technology would be in compliance with applicable provisions under 45 CFR part 170. EHR technology with certified capabilities generally have clear advantages because many of the certification requirements are aimed toward ensuring interoperable data sharing and enabling processes to keep electronic data confidential and reliable. In particular, all EHR technology certified under the ONC Health IT Certification Program is required to meet certain privacy and security protection requirements for an individual's health information.[24] 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.

B. Use of EHRs Not Certified by ONC

EHRs not certified by ONC can also 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. Specifically, for EHRs not certified by ONC, sponsors should consider whether such systems have adequate controls in place to ensure that the confidentiality, integrity, and reliability of data are preserved. To ensure the confidentiality, integrity, and reliability of data, 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 (see section VI.C of this guidance)
- Records are available and retained for FDA inspection for as long as the records are required by applicable regulations (see section VII of this guidance)

Sponsors should consider these factors when determining the suitability of EHRs not certified by ONC for use in clinical investigations. If the clinical investigation site is using a system that

[22] See the ONC Health IT Certification Program at https://www.healthit.gov/policy-researchers-implementers/onc-health-it-certification-program and the Department of Health and Human Services' final rule entitled "2015 Edition Health Information Technology (Health IT) Certification Criteria, 2015 Edition Base Electronic Health Record (EHR) Definition, and ONC Health IT Certification Program Modifications," (October 16, 2015, 80 FR 62602).

[23] See 80 FR 62602. Also see the Federal Health IT Strategic Plan (2015–2020) at https://www.healthit.gov/policy-researchers-implementers/health-it-strategic-planning, and select http://www.healthit.gov/sites/default/files/9-5-federalhealthitstratplanfinal_0.pdf.

[24] See 45 CFR 170.314(d)(1) through (8) and 170.315(d)(1) through (10).

does not contain the adequate controls previously described in the bulleted items, 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).

VI. OTHER GENERAL CONSIDERATIONS FOR BEST PRACTICES

When using data from EHRs in clinical investigations, sponsors and clinical investigators should also adhere to the best practices discussed in this section.

A. Use of EHRs in Clinical Investigations

Use of EHRs as a source of data in clinical investigations 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. This should include a description of how the relevant EHR data are extracted and subsequently imported into the sponsor's electronic system. Sponsors 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 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. They should also consider the clinical investigator's ability to appropriately archive and backup any EHR data that may be used for the clinical investigation so that data are not lost before the record retention period (see section VII of this guidance).[25] Sponsors should also ensure that study monitors have suitable access to all relevant subject information pertaining to a clinical investigation as appropriate. Such access must be described in the informed consent (see 21 CFR 50.25(a)(2)) (see section VI.D of this guidance). Furthermore, 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.

B. Data Modifications

[25] If the necessary records are not available, FDA may not accept the study data in support of an IND or an application for marketing approval. If the records exist, but a sponsor or an applicant cannot disclose them to FDA because such disclosure is prohibited by applicable foreign law, the sponsor or applicant may seek a waiver of this requirement (21 CFR 312.120(c)). For FDA to rely on such data that cannot be disclosed, the sponsor and FDA would need to agree on an alternative validation procedure. For more information, see FDA's guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND; Frequently Asked Questions*.

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 sponsor's electronic system should capture any updated information as well as any accompanying audit trail information.

C. Audit Trails

For EHR data gathered during the course of a clinical investigation, sponsors and clinical investigators should 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 clinical investigation. Identification of the data originator (i.e., EHR or study personnel entering or modifying the clinical study data) and the date and time data were entered into the EHR should be available to FDA at the time of inspection (see section IV of this guidance). 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 (see 21 CFR 312.58, 312.68, and 812.145) (see section VII of this guidance).

D. Informed Consent

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 (see 21 CFR 50.25(a)(5)).[26] The extent of access to EHRs granted to other parties, such as sponsors, contract research organizations, and study monitors, must also be described (see 21 CFR 50.25(a)(5)). Sponsors should consider whether there are any reasonably foreseeable risks with the use of EHRs, such as those involving an increased risk of data breaches, that must be described to the subject in the informed consent (see 21 CFR 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.

E. Privacy and Security of Data

When using data from EHRs in clinical investigations, sponsors should 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.[27] Clinical investigators should comply with any privacy and security requirements applicable to their institution or organization.

[26] For more information, see the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet.* When final, this guidance will represent FDA's current thinking on its informed consent regulations.

[27] For more information, see FDA's guidance for sponsors, clinical investigators, and IRBs *Data Retention When Subjects Withdraws From FDA-Regulated Clinical Trials.*

VII. INSPECTION, RECORDKEEPING, AND RECORD RETENTION REQUIREMENTS

FDA must have access to records and may inspect and copy all records pertaining to a clinical investigation in accordance with 21 CFR 312.57, 312.58, 312.62, 312.68, 812.140, and 812.145. Likewise, when the EHR is identified as the source,[28] all relevant data within the EHR pertaining to the clinical investigation must be made available to FDA for review upon request (see 21 CFR 312.62(b), 312.68, 812.140(a), and 812.145). During an inspection, FDA may also request other paper or electronic records to support data in the eCRF (e.g., case histories, other data pertaining to the clinical investigation) (see 21 CFR 312.57, 312.58, 312.62(b), 312.68, 812.140(a)(3), and 812.145).[29]

Clinical investigators must retain all paper and electronic source documents (e.g., originals, certified copies)[30] and records as required to be maintained in compliance with 21 CFR 312.62(c) and 812.140(d). For human drugs and biological products, clinical investigators must retain all records (e.g., including EHRs pertaining to a clinical investigation), as required by 21 CFR part 312, for 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. For medical devices, an investigator or sponsor must maintain all records, including EHRs relating to the investigation, as required by 21 CFR 812.140(d), for 2 years after the latter 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 the purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

[28] The review of source data by FDA 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 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. For more information, see FDA's *eSource guidance.*

[29] In addition, in the United States, under the Department of Health and Services' final rule entitled "Standards for Privacy of Individually Identifiable Health Information" privacy rule (December 28, 2000, 65 FR 82462) (also referred to as the HIPAA privacy rule), FDA does not need permission to inspect records containing health information (see 45 CFR 164.512).

[30] *Certified copy* is 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. For more information, see FDA's guidance for industry *Electronic Source Data in Clinical Investigations.*