Jeffrey K. Shapiro Director
jshapiro@hpm.com
Hyman, Phelps & McNamara, P.C., Washington, DC

The use of electronic health record data in clinical investigations

On 19 July 2018, the U.S. Food and Drug Administration ('FDA') announced their latest guidance, Use of Electronic Health Record Data in Clinical Investigations ('EHR Guidance'). Providing recommendations for clinical trial sponsors on the permissible use of electronic health records ('EHRs') in FDA-regulated clinical investigations, a major challenge remains with the change from paper to digital - that adoption is voluntary and consequently, record-keeping varies in the industry. Jeffrey K. Shapiro, Director at Hyman, Phelps & McNamara, P.C., provides insight into the recommendations and the best practices in using the EHR Guidance - and its significance for those wanting to investigate further.

Slowly but surely, the FDA is adapting its record-keeping expectations for the digital world. Most of the relevant regulations date back several decades and were adopted in a world in which the healthcare industry, manufacturers and government bureaucracies all relied on paper records. That world is fast disappearing and all parties are scrambling to keep pace.

This July, the EHR Guidance was published. This aims to clarify the permissible use of EHRs in FDA-regulated clinical investigations. Those who may find the EHR Guidance useful include study sponsors, clinical investigators, contract research organisations and institutional review boards ('IRBs'). The FDA recognises that the use of EHRs in clinical investigations may have benefits such as allowing greater accuracy, easier real time review and more opportunities for long term follow up.

The EHR Guidance was issued jointly by the drug, device and biologic centres within the FDA, so it applies to the full range of products typically the subject of clinical investigations in order to support clearance or approval[1]. The FDA also consulted the lesser-known Office of the National Coordinator for Health Information Technology ('ONC') within the Department of Health and Human Services ('HHS'). The ONC was created just a few years ago to help lead the national computerisation of health records. Perhaps the greatest challenge in issuing guidance like this, is the de-centralised nature of EHRs. The technology is voluntarily adopted by healthcare providers in many different types and flavours, depending upon the particular vendor and the needs of a facility. Some are interoperable and some are not. The ONC does not have regulatory authority, but operates a voluntary certification program intended to encourage interoperability and minimum levels of security and privacy.

The EHR Guidance intelligently recognises that the FDA does not control all the players. In particular, the FDA does not generally regulate the healthcare facilities and practitioners who onerate EHRs. Rather, the FDA's regulatory purview is over the conduct of clinical investigations of new drugs and devices[2]. These regulations cover the conduct of the sponsors and investigators, including record-keeping requirements that generally apply to the importation of data from EHRs into study records. Additionally, the FDA regulates the process of informed consent by study subjects[3]. As we shall see in the discussion below, the use of EHRs has interesting implications for informed consent. The FDA also regulates IRBs, although that frankly does not seem to loom large in the current topic of incorporating EHRs in clinical investigations[4]. Finally, the FDA has authority allowing it to inspect and copy records relating to a clinical investigation[5]. Consistent with the FDA's authority, the recommendations in the EHR Guidance are focused on clinical trial sponsors and the use of data from EHRs at study sites. Specifically, it 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 electronic data capture ('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 the FDA's inspection, record-keeping, and record retention requirements[6].

The recommendations refer to the FDA's regulatory requirements for record-keeping and also inspections but are not overly prescriptive in how these requirements must be met. They address the use of EHR data in prospective clinical investigations, including those conducted in foreign countries[7].

The FDA also refers to 2013 guidance on the use of Electronic Source Data In Clinical Investigations[8] ('ESD Guidance'). The ESD Guidance explains how

Image: Chin Leong Teoh / EyeEm / EyeEm / Getty Images

continued

source data can be used to populate an electronic case report form ('eCRF'). In the EHR Guidance, the FDA identifies EHRs as potential source data for an eCRF, making recommendations to ensure the quality of the data entering the eCRF. The recommendations broadly cover interoperability and integration of systems, best practices for use of EHRs in clinical investigations and inspection, record-keeping and record retention requirements. We turn now to a detailed discussion of each topic, followed by closing thoughts[9].

Interoperability and integration of systems

The FDA recognises that EHR and EDC systems may be non-interoperable, interoperable, or fully integrated. The EHR Guidance recognises the benefits of interoperability, such as reducing manual data entry errors, simplifying data collection and improving data quality and efficiency in clinical investigations. The FDA recommends using systems that leverage existing open data standards, when possible, while ensuring that the integrity and security of data are not compromised.

The FDA also encourages exchange of structured data "so that data may be entered once at the pointofcare and used many times without manual reentry or manual source data verification.[10]"

The FDA does caution that extraction and exchange of unstructured data (e.g. free form text) may have reliability problems and strongly hints that such data should not be used as critical source data, such as a study endpoint, unless extraordinary efforts are made to ensure the reliability and quality of the data.

If systems are intended to be interoperable, a sponsor must validate consistent and repeatable transmission of accurate data from EHRs to the sponsor's EDC system. After such validation, the FDA reminds sponsors to ensure that EHR software updates during an investigation, do not later alter the integrity and security of the transferred data. Sponsors are also encouraged to periodically validate a subset of extracted EHR data transferred to an EDC system for accuracy, consistency and completeness.

If an EHR system is interoperable with multiple EHR systems from different organisations not affiliated with a clinical investigation site, the FDA nonetheless permits integration of these data at the clinical investigation site. The FDA reminds sponsors that there must be appropriate data sharing agreements in place.

Best practices for using EHR systems in clinical investigations

ONC Certification

A point of emphasis in the EHR Guidance is leveraging the ONC's certification program. By way of background, ONC has established a voluntary certification program for healthcare information technology. Under this program, EHR technology can be certified, if it complies with certain regulatory provisions facilitating interoperability and ensuring privacy and security protection for an individual's health information[11]. The FDA expects sponsors to document the specific manufacturer, model and version number of EHR systems providing data in clinical investigations, as well as noting whether they are ONC-certified or not. It is permissible to use a non-certified EHR system. If, however, such a system is not used, the FDA expects that a sponsor will address the privacy and security controls in place to ensure the confidentiality, integrity and security of the data. The following factors are called out:

- policies and processes for the use of EHR systems at the clinical investigation site are in place, and there are appropriate security measures employed to protect the study data;
- access to electronic systems is limited to authorised 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.

A sponsor must address each of these factors. If adequate controls are not in place, then the sponsor must address the risk of employing a particular EHR system. The FDA notes that in some cases, authorising bodies outside the US may have evaluated an EHR system, and/or vendors may have relevant feature and product-specific information.

eSource Principles for EHRs

Under 21 CFR Part 11 ('Part 11'), manufacturers and other FDA regulated firms must implement controls,

1. The drug centre is the Center for Drug Evaluation and Research ('CDER'). The biologics centre is the Center for Biologics Evaluation and Research ('CBER'). The device centre is the Center for Devices and Radiological Health ('CDRH').
2. 21 CFR Part 312 (drugs); Part 812 (devices).
3. 21 CFR Part 50.
4. 21 CFR Part 56.
5. Federal Food, Drug, and Cosmetic Act ('FFDCA') § 704(a)(1); 21 CFR 312.62, 312.68, 812.40, 812.145.
6. EHR Guidance, p.2.
7. Ibid, pp. 23.
8. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm328691.pdf, p. 4
9. This discussion is based on the EHR guidance, pp. 510.
10. Ibid, p.5.
11. 45 CFR Part 170.

Sponsors must specifically tell subjects that the FDA may inspect records without a subject's permission. The guidance notes that the FDA generally will not copy records that include a subject's name, and when it does so, it will treat the name as confidential.

including audits, system validations, audit trails, electronic signatures, and documentation for software and systems involved in processing the electronic data that the FDA record-keeping rules require them to maintain. In the EHR Guidance, the FDA indicates that Part 11 does not apply to EHS systems. Rather, it applies only to the sponsor's EDC system. This approach makes sense, because it would be unworkable to ask all healthcare facilities and practitioners generating EHR data to comply with Part 11.

The EHR Guidance undertakes to clarify how Part 11 compliance interacts with Part 11. For instance, to the extent that Part 11 requires a sponsor to identify a data originator, the HER Guidance notes that identifying an EHR system as the data originator may be sufficient, without details about all users who contribute information to a patient's EHR.

After data is transmitted to an eCRF, the clinical investigator or delegated personnel should be the only persons authorised to make changes. The EHS system or users should not be authorised to alter an eCRF.

Blinded Study Designs

The EHR Guidance reminds sponsors to consider whether the use of interoperable EHR and EDC systems has any potential to unblind the treatment allocation. If so, a sponsor should put appropriate controls in place.

Informed Consent

The EHR Guidance covers the impact of EHRs on informed consent; a point that could easily be overlooked. The basic admonition is for the sponsor to include in an informed consent, a statement describing the extent of confidentiality of records that identify a subject and the entities that may gain access to a subject's EHR. In a world of digital transfer, there is much more opportunity for a patient's data to be transferred to a number of different parties. The FDA's position is that a patient entering a clinical investigation must know upfront who these parties will be.

Sponsors must specifically tell subjects that the FDA may inspect records without a subject's permission. The guidance notes that the FDA generally will not copy records that include a subject's name, and when it does so, it will treat the name as confidential.

Nonetheless, on rare occasions, such as may involve a court case, the FDA may be required to disclose this information to third parties. Therefore, an informed consent should not promise absolute confidentiality by the FDA.

Inspection, record-keeping, & record retention requirements

FDA makes clear in the guidance that the use of EHR/EDC/eCRF systems for record-keeping does not negate the FDA's access to records as required by law. All relevant EHR-based information must be available and viewable by the FDA as original records in the her, or as certified copies.

These records and/or copies can be maintained electronically. The FDA also asserts that it is entitled to review the EHR audit trail information during an inspection. Although the retention times are not strictly speaking unique to digital records, the FDA reminds sponsors that records for studies of human drugs and biological products must be maintained for two years following marketing approval or notification to the FDA that the investigation was discontinued. For devices, the retention time is two years after the later of the date the investigation is terminated or completed or the records are no longer required to support a marketing application.

Closing thought

The EHR Guidance marks the FDA's continuing effort to update its procedures and practice for the digital age. The guidance shows that the FDA is open to the use of data transferred to clinical trial records from EHRs, whether manually or by seamless integration. It is clear that the FDA has thought through the major issues involved. The EHR Guidance has many useful recommendations that will help sponsors ensure compliance. Although these recommendations are fairly general, that is actually a good thing. If the recommendations were too detailed, they might soon be obsolete and sponsors might also find it difficult to apply them to the wide variety of circumstances they may encounter.

These recommendations appear well-crafted to stand the test of time. A thoughtful sponsor will carefully consider the FDA's recommendations when planning for the use of EHR data in clinical investigations.