

Agency Guidance Snapshot: Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations – Questions and Answers (Draft Guidance)

The Yale Human Research Protection Program (HRPP) has launched the “Agency Guidance Snapshot” series. The purpose of the Agency Guidance Snapshots is to highlight recent agency guidance from the Food and Drug Administration (FDA)¹, Office for Human Research Protections (OHRP), and other federal agencies that specifically impacts Yale University and affiliate stakeholders who conduct or oversee *human subjects research*.

Please Note: Yale University does not expect any immediate changes to policies due to this guidance; however, this guidance will be taken into consideration as policies and procedures are reviewed and revised in the future. Yale University may have additional requirements related to the topics covered in this guidance. For more information, please refer to the following Yale University Human Research Protection Program (HRPP) documents located on the HRPP website ([Policies, Procedures, Guidance, and Related Documents](#)) and in the Yale HRPP IRES-IRB Library ([IRES IRB LOGIN](#)): 1) [Yale HRPP Policy and Standard Operating Procedure Manual](#); 2) [Yale HRPP Investigator Manual](#); 3) [Yale IRB Members and Chairs Manual](#); and 4) [HRPP Supplemental Guidance Manual](#). Please also refer to [University Policies & Procedures](#) and policies published by the various Yale University schools and departments.

Title of Document:	Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations – Questions and Answers (Draft Guidance)
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Hyperlink to Document:	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions

Overview of Guidance Document:

This document provides guidance to sponsors, clinical investigators, institutional review boards (IRBs), contract research organizations (CROs), and other interested parties on the use of electronic systems, electronic records, and electronic signatures in clinical investigations of medical products, foods, tobacco products, and new animal drugs. The guidance provides recommendations regarding the requirements, including the requirements under 21 CFR part 11, under which FDA considers electronic systems, electronic records, and electronic signatures to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

¹ FDA Guidance documents represent the Agency's current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Background on Electronic Systems in Clinical Investigations

FDA recognizes that since 2003 (when FDA issued initial guidance on Part 11 compliance), advances in technology have expanded the uses and capabilities of electronic systems in clinical investigations. In addition, electronic systems and technologies are used and managed in novel ways, services are shared or contracted between organizations, and the electronic data flow between systems is more efficient and more prevalent. The capabilities of electronic systems have improved, and features such as automated date and time stamps, audit trails, and the ability to generate complete and accurate copies and to archive records are standard components of many electronic systems. Understanding the evolving uses of electronic records, electronic systems, and electronic signatures in clinical investigations is important for FDA in its assessment of the authenticity, integrity, and reliability of data submitted in support of marketing applications or submissions.

Key Points for Researchers, IRB/HRPP Staff, Chairs, & Members:

Electronic records used in clinical investigations that fall under the scope of part 11 requirements include:

- Records needed for FDA to reconstruct a clinical investigation that are maintained and archived under predicate rules in electronic format in place of paper format or where the electronic record is relied on to perform regulated activities.
- Records submitted to FDA in electronic format under predicate rules, even if such records are not specifically identified in FDA regulations.

The FDA guidance document includes the following Q&As related to **electronic records**, which may be beneficial for our research community to understand. Detailed answers to the questions below can be found in the [full guidance document](#):

- **Q1:** Are electronic records from real-world data sources submitted to FDA as part of marketing application or under other predicate rules subject to part 11 requirements?
- **Q2:** If a sponsor is conducting a clinical investigation with a non-U.S. (foreign) site, are the electronic records submitted to FDA as part of a marketing application or under other predicate rules subject to part 11 requirements?
- **Q3:** Should sponsors, clinical investigators, and other regulated entities maintain and retain a certified copy of clinical investigation electronic records?
- **Q4:** Is FDA recommending that electronic records from medical service providers not involved in the clinical investigation be certified?
- **Q5:** How should sponsors, clinical investigators, and other regulated entities retain electronic records from a clinical investigation?
- **Q6:** Are electronic communication methods (e.g., email systems or text messages) for transmitting electronic records addressed by 21 CFR part 11?

Electronic systems owned or controlled by sponsors or other regulated entities and are used by such regulated entities to produce required records in clinical investigations may include the following:

- Electronic case report forms (eCRFs) and electronic data capture (EDC) systems, including EDC systems that capture source data directly into eCRFs
- Electronic trial master files (eTMFs)
- Electronic clinical data management systems (eCDMS)
- Electronic clinical trial management systems (eCTMS)

- Electronic quality management systems
- Interactive response technology (IRT) systems
 - Interactive voice response system (IVRS)
 - Interactive web response system (IWRS)
- Electronic IRB management systems
- Electronic informed consent (eIC) systems
- Centralized, web-based portals that display, maintain, and archive essential data (i.e., electronic patient-reported outcomes (ePROs), electronic clinical outcome assessments (eCOAs), DHT-collected patient data (see section III.D), or eIC documents and records)
- Adverse event reporting (AER) and processing systems

The FDA guidance document includes the following Q&As related to **electronic systems owned or controlled by sponsors or other regulated entities**, which may be beneficial for our research community to understand. Detailed answers to the questions below can be found in the [full guidance document](#):

- **Q7:** What should be considered when using a risk-based approach for validation of electronic systems used in clinical investigations?
- **Q8:** What documentation should the sponsor have in place for electronic systems that fall under the scope of part 11, and what will be FDA's focus during inspections of the sponsor?
- **Q9:** What documentation should be available at clinical investigator sites for electronic systems that fall under the scope of part 11, and what will be FDA's focus during inspections of clinical investigator sites?
- **Q10:** During an inspection, will FDA review the reports of audits performed by sponsors or other regulated entities of IT service providers' electronic systems, products, and services?
- **Q11:** What are FDA's requirements and recommendations regarding the use of security safeguards?
- **Q12:** What are considerations for sponsors and other regulated entities when implementing audit trails?
- **Q13:** Should an audit trail record every key stroke?
- **Q14:** What controls should be in place to ensure that the electronic system's date and time are correct?
- **Q15:** What are the requirements and recommendations regarding training of individuals who use electronic systems in clinical investigations?
- **Q16:** Does FDA provide preliminary evaluations of electronic systems to be used in a clinical investigation to determine whether they comply with part 11 requirements?

Sponsors and other regulated entities can contract with vendors to provide IT (Information Technology) services for a clinical investigation (e.g., data hosting, cloud computing software, platform and infrastructure services). Sponsors and other regulated entities are responsible for ensuring that electronic records meet applicable part 11 regulatory requirements. **When determining the suitability of the IT service and IT service provider, sponsors and other regulated entities should consider the following regarding the IT service provider's ability to ensure the authenticity, integrity, and confidentiality of clinical investigation records and data:**

- Policies the IT service provider has in place to allow the sponsor to perform oversight of the clinical investigation functions provided by the IT service provider.
- Processes and procedures the IT service provider has in place for validation of specific IT services to be used in the clinical investigation (see Q7).

- Ability of the IT service provider to generate accurate and complete copies of records and to provide access to data for as long as the records are required to be retained by applicable regulations (see Q5).
- Processes and procedures the IT service provider has for retaining records and making them available for FDA inspection for as long as the records are required to be retained by applicable regulations (see Q5).
- Access controls used by the IT service provider for specific IT services used in the clinical investigation, including SOPs for granting and revoking access (see Q11).
- Ability of the IT service provider to provide secure, computer-generated, time-stamped audit trails of users' actions and changes to data (see Q12).
- Ability of the IT service provider to secure and protect the confidentiality of data at rest and in transit (as appropriate for the content and nature of the record).
- Processes and procedures the IT service provider has in place related to electronic signature controls (see section III.E).
- Relevant experience of the IT service provider

The FDA guidance document includes the following Q&As related to **contracting IT (Information Technology) services for a clinical investigation**, which may be beneficial for our research community to understand. Detailed answers to the questions below can be found in the [full guidance document](#):

- **Q17:** Should sponsors or other regulated entities establish service level agreements with IT service providers?
- **Q18:** What should sponsors and other regulated entities have available to demonstrate that the IT services are performed in accordance with FDA's regulatory requirements?
- **Q19:** Would FDA inspect or investigate IT service providers in a clinical investigation?

For the purposes of this guidance, a Digital Health Technology (DHT) is a system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. DHTs may take the form of hardware and/or software. In many instances, DHT software may run on general-purpose computing platforms (e.g., mobile phone, tablet, or smart watch). **Sponsors, clinical investigators, and other regulated entities can use DHTs to record and transmit data during a clinical investigation.**

The FDA guidance document includes the following Q&As related to **DHTs**, which may be beneficial for our research community to understand. Detailed answers to the questions below can be found in the [full guidance document](#):

- **Q20:** When using DHTs to capture data from participants in clinical investigations, how do sponsors identify the data originator?
- **Q21:** How should data attribution be ensured when DHTs are used to capture, transmit, and record data in clinical investigations?
- **Q22:** What should be considered during the initial transfer of the data from a DHT to the durable electronic data repository?
- **Q23:** What is the location of the source data collected by a DHT, and what DHT-collected data would FDA intend to inspect during an inspection?

An electronic signature is a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature. In general, electronic signatures and their associated electronic records that meet all applicable requirements under part 11 will be considered to be equivalent to handwritten signatures.

Part 11 specifies that signed electronic records must contain the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature. In addition, electronic signatures must be linked to the respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

In situations where electronic signatures cannot be placed in a specified signature block, a statement of testament (e.g., “I approved the contents of this document”) should be placed elsewhere in the document to state the meaning of the signature and link the signature to the electronic record.

The FDA guidance document includes the following Q&As related to **electronic signatures**, which may be beneficial for our research community to understand. Detailed answers to the questions below can be found in the [full guidance document](#):

- [Q24](#): What methods might be used to create valid electronic signatures?
- [Q25](#): Does FDA consider signatures drawn with a finger or an electronic stylus on a mobile platform or other electronic system to be electronic signatures?
- [Q26](#): How should sponsors and regulated entities verify the identity of the individual who will be electronically signing records as required in § 11.100(b)?
- [Q27](#): What requirements must an electronic signature based on biometrics meet to be considered acceptable?
- [Q28](#): Does FDA certify electronic systems and methods used to obtain electronic signatures?

For more related information, please see the following links to additional resources:

- [FDA Website – Regulatory Information](#)
- [Clinical Trails Transformation Initiative Resources – Electronic Healthcare Data](#)