acdm

association for **clinical data management**

FDA Q&A guidance on Electronic systems, Electronic Records and Electronic Signatures in Clinical Investigations. Points to Consider from ACDM DMEG Regulatory Considerations group

Authors: Silvia Pérez, Linda Shostak, Julianne Hull, Akinlolu Fasanmi & Evaldas Lebedys

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers Guidance for Industry

Regulatory Context

The FDA enacted 21 Code of Federal Regulation (CFR) Part 11 Electronic Records, Electronic Signatures in 1997 to address emerging use of electronic systems and signatures in contrast to traditional paper-based records and wet ink signatures.

In 1999 FDA issued Guidance for Industry - COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS to further clarify expectations for systems used to create, modify, maintain, archive, retrieve or transmit clinical data intended for FDA submission. This guidance defined expectations for use of SOPs, audit trails, system security and controls.

As use of electronic signatures and systems continued to escalate the FDA issued Part 11, Electronic Records; Electronic Signatures - Scope and Application in 2003 to address concerns that implementation of 21 part 11 could restrict adoption of electronic technology, impede innovation and increase compliance costs.

In 2013 the FDA again responded to advances in technology and adoption of electronic source data capture by issuing the Electronic Source Data in Clinical Investigations which addressed expectations for identifying data originators and investigator review and retention of electronic data.

FDA has responded to increasing use of electronic systems to support decentralized trials and direct data collection by issuing guidance clarifying expectations for validation and controls over systems. This includes the 2023 Digital Health Technologies for Remote Data Acquisition in Clinical Investigations and the 2024 Conducting Clinical Trials With Decentralized Elements guidance.

This brings us to the current Questions and Answers document Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers which was published in Oct 2024. Per the Federal Register Notice "the goals of the guidance are to: (1) update recommendations for applying and implementing data integrity and data security controls, including the use of audit trails and the protection of records in the current environment of electronic systems used in clinical investigations; (2) expand upon recommendations on the risk-based approach to validation of electronic systems described in the guidance for industry "Part 11, Electronic Records; Electronic Signatures—Scope and Application" (August 2003); (3) provide recommendations on using information technology service providers to provide services during a clinical investigation; (4) provide recommendations regarding the collection of data through digital health technologies; (5) facilitate the use of electronic signatures; and (6) facilitate the use of electronic systems, electronic records, and electronic signatures to improve the quality and efficiency of clinical investigations. "

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers Guidance for Industry

It is important to note that this guidance supersedes the guidance for industry entitled "Computerized Systems Used in Clinical Investigations" issued in May 2007.

In the Introduction FDA states the Q and A is intended to provide guidance to sponsors, clinical investigators, IRBs, 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.

Expands on recommendations in the August 2003 Part 11, Electronic Records; Electronic Signatures – Scope and Application.

The Background provides a brief history of 21 Part CFR 11 guidance including the 1997 CFR publication and the 2003 Part 11, Electronic Records; Electronic Signatures - Scope and Application Guidance for Industry which clarified questions regarding 21 Part 11. The recommendations in the 2003 guidance reflected the technology available at that time.

FDA notes this 2024 Q and A is:
Intended to address advances in technology including the way in which systems and technologies are used and managed (i.e. shared or contracted between organizations with increased capability and improved data flow) and provide additional recommendations based on risk-based approaches to validation.

The guidance also addresses applicability of 21 Part 11 for use of digital health technology (DHT) to remotely acquire data.

Section III contains 29 questions and their answers for Electronic Records, Electronic Systems Deployed by Regulated Entities, Information Technology Service Providers and Services, Digital Health Technologies and Electronic Signatures topics. Many of the questions describe the FDA recommendation for risk-based approaches to validation and oversight of electronic systems in alignment with ICH E6 and E8.

ACDM Regulatory considerations DMEG reviewed all 29 questions and answers and identified key changes or highlights of interest or potential impact on data management. Each question was mapped to key topic areas in Appendix 1 Q and A which includes hyperlinks to the questions.

Appendix 1 Q and A Grid

	Question #	Real World Data\EHR	Records Subjects to Part 11	Certified Copies	Retention	Validation	Inspections & Audits	Security	Audit Trails	Training	IT Service	DHT	Data Originator	eSignature
	ELECTRONIC RECORDS													
1	Are electronic records from real-world data sources submitted to FDA as part of a marketing application or under other predicate rules subject to part 11 requirements?	■	■											
2	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?		■											
3	Should regulated entities maintain and retain a certified copy of clinical investigation electronic records?			■	■									
4	Is FDA recommending that electronic records from medical service providers not involved in the clinical investigation be certified?	■		■										
5	How should regulated entities retain electronic records from a clinical investigation?				■									
6	Are electronic communication methods (e.g., email systems or text messages) addressed by 21 CFR part 11?		■											
7	What should be considered when using a risk-based approach for validation of electronic systems deployed in clinical investigations?					■								
8	What will be FDA's focus during inspections of the sponsor for electronic systems that fall under the scope of part 11, and what documentation should the sponsor have in place for such systems?		■		■	■	■	■	■	■	■			

	Question #	Real World Data\EHR	Records Subjects to Part 11	Certified Copies	Retention	Validation	Inspections & Audits	Security	Audit Trails	Training	IT Service	DHT	Data Originator	eSignature
9	What will be FDA's focus during inspections of clinical investigators for electronic systems that fall under the scope of part 11?						■			■				
10	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?						■							
11	What are FDA's requirements and recommendations regarding the use of security safeguards for electronic systems deployed by regulated entities?							■						
12	What are FDA's expectations for the use of audit trails by regulated entities?				■				■					
13	Should an audit trail record every key stroke?								■					
14	What controls should be in place to ensure that the electronic system's date and time are correct?							■	■					
15	What are the requirements and recommendations regarding training of individuals who use electronic systems in clinical investigations?									■				
16	Does FDA provide preliminary evaluations of electronic systems to be used in a clinical investigation to determine whether they comply with part 11 requirements?							■						
	INFORMATION TECHNOLOGY SERVICE PROVIDERS & SERVICES													
17	What should regulated entities include in agreements with IT service providers?										■			
18	What should regulated entities have available to demonstrate that the IT services are performed in accordance with FDA's regulatory requirements?							■			■			

	Question #	Real World Data\EHR	Records Subjects to Part 11	Certified Copies	Retention	Validation	Inspections & Audits	Security	Audit Trails	Training	IT Service	DHT	Data Originator	eSignature
19	Would FDA inspect or investigate IT service providers in a clinical investigation?						■				■			
	DIGITAL HEALTH TECHNOLOGIES													
20	When using DHTs to record data from participants in clinical investigations, how do sponsors identify the data originator?							■	■			■	■	
21	How should data attribution be ensured when DHTs are used to record and transmit data in clinical investigations?							■		■		■	■	
22	What should be considered during the transfer of the data from a DHT to the durable electronic data repository?					■			■			■		
23	For inspection purposes, what is the location of the source data recorded by a DHT?						■					■		
	ELECTRONIC SIGNATURES													
24	What methods might be used to create valid electronic signatures?					■		■						
25	Does FDA consider signatures drawn with a finger or an electronic stylus on a mobile platform or other electronic system to be electronic signatures?													■
26	How should regulated entities verify the identity of the individual who will be electronically signing records as required in part 11.100(b)?							■						■
27	What requirements must an electronic signature based on biometrics meet to be acceptable?							■						■
28	Does FDA certify electronic systems and methods used to obtain electronic records?						■	■	■					■
29	Are users of electronic signatures required to submit letters of non-repudiation to FDA to certify that an electronic signature is the legally binding equivalent of a traditional handwritten signature?													■

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers Guidance for Industry

Q1 Are electronic records from real-word data submitted to FDA as part of marketing applications or under other predicate rules subject to part 11 requirements?

"FDA does not intend to assess compliance of electronic health record (EHR) or other electronic systems that are sources of real-world data (RWD)"

However, "once the electronic records enter the sponsor's EDC system FDA will assess compliance with part 11"

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?

The sponsor must ensure data submitted in support of a marketing application is credible and accurate. "For clinical investigations conducted at sites outside of the United States and not under an IND, IDE or INAD the quality, integrity and authenticity of the data submitted to the FDA should be equivalent to that of data collected under an IND, IDE, INAD"

Q3 Should regulated entities maintain and retain a certified copy of clinical investigation electronic records?

"The retention period of certified copies maintained and retained in place of original records is the same as for original records"

When providing certified electronic or paper copies of electronic records the metadata should be included (e.g. date and time stamp, audit trial of changes).

Q4 Is FDA recommending that electronic records from medical service providers not involved in the clinical investigation be certified?

"No. FDA is not recommending certification for electronic copies of records from medical service providers such as hospitals, laboratories, or health care practitioners not involved in the clinical investigation"

Q5 How should regulated entities retain electronic records from a clinical investigation?

FDA recognizes that there are various ways to retain electronic records including electronic storage devices and cloud computing services.

The retention method must ensure authenticity, integrity, confidentiality and the meaning of the record are preserved. "The electronic records and all metadata should be preserved in a secure and traceable manner"

Electronic records must be maintained for the applicable retention period and must be available for inspection. "When records exist only in electronic format, sufficient backup and recovery procedures should be in place to protect against data loss"

"FDA may request that regulated entities provide all records and data needed to reconstruct a clinical investigation including associated metadata and audit trails"

FDA may request copies of records and data in human-readable form.
"When systems are decommissioned and cannot be recommissioned or a contract with a hosted system ends, sponsors should ensure the metadata are obtained and retained and can be linked to each corresponding data element."

Q6 Are electronic communication methods (e.g. email systems or text messages) addressed by 21 CFR part 11?

No. Part 11 does not address electronic communication methods
Regulated entities should determine if the electronic communication method is appropriately secure for the type of data being transmitted and consider other requirements related to participant privacy

Electronic Systems Deployed by Regulated Entities
"Regulated entities should ensure that systems are fit for purpose and implemented in a way that is proportionate to the risks to participant safety and reliability of trial results.

Recommendations for systems deployed "in clinical investigations to create, modify, maintain, archive, retrieve, or transmit clinical investigation records."

Examples include but are not limited to systems used for randomization, data collection, collection and processing of adverse event reports, informed consent and medical product dispensation

Q7 What should be considered when using a risk-based approach for validation of electronic systems deployed in clinical investigations?

For this guidance the term validation, including user acceptance testing, is a process to establish and document that the specified requirements of the system can be fulfilled from design until decommissioning or transition to a new system.

The level of validation may depend on the nature of the system (i.e. bespoke or custom systems versus systems where no alterations are needed).

FDA recommends taking a risk-based approach to validating electronic systems
Considerations for risk-based validation include:

- Intended use of the system
- The purpose and importance of the data or records that are collected, generated, maintained, ` or retained in the system
- The potential of the system to affect the rights, safety and welfare of participants or the relegation of the trial results
- Validation should encompass system functionality, protocol specific configurations, customizations, data transfers and interfaces between systems (e.g. interoperability and communication)

- If validation is performed by an IT service provider, the regulated entity that deploys the system can consider using the IT service provider's documentation to evaluate whether the system is fit for purpose including
  - Processes for developing and managing the system
  - Validation processes
  - Functional testing of the electronic systems
  - Change control procedures and tracking logs

FDA may request documentation of system validation during an inspection (applies to validation conducted by and on behalf of the sponsor).

The regulated entity must ensure such documentation is available, this includes documentation created and maintained by the IT service provider.

Q8 What will be FDA's focus during inspections of the sponsor for electronic systems that fall under the scope of part 11, and what documentation should the sponsor have in place for such systems?

FDA will generally focus on:

- Data collection, data handling, data security, and data management plans and procedures
- The life cycle of the electronic system, from design and implementation to decommissioning or transitioning to a new system
- Processes and procedures to ensure that the data and records are not altered in value or meaning,
- Processes and procedures to ensure appropriate access to electronic systems
- Change control procedures
- Relevant contracts with IT service providers or other contracted entities that detail their functions and responsibilities
- Corrective and preventive actions implemented to address errors and noncompliance

"Documentation should include a diagram that depicts the flow of data from data creation to final storage of data"

FDA notes sponsors may take a risk-based approach similar to that taken to validation when determining if documentation or SOPs are appropriate:

Q9 What will be FDA's focus during inspections of clinical investigators for electronic systems that fall under the scope of part 11?

FDA will generally focus on the following issues related to electronic systems:

- Records related to staff training
- Procedures and controls for system access, data creation, data modification and data maintenance
- Documentation regarding the use of the systems including that users have their own accounts and appropriate access, that sponsors are notified of changes in trial personnel so that access can be revoked and that any backup, recovery or contingency plans for source records have been used

If the clinical investigator deploys their own electronic system to create, modify, maintain, retain or transmit electronic records (e.g. an EDC deployed by the clinical investigator, or an electronic investigator site file) the investigators must retain the documentation described in Q8 and make it available during inspection.

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?

"FDA will generally not review audit reports of the IT service provider's electronic systems, products and services"

Q11 What are FDA's requirements and recommendations regarding the use of security safeguards for electronic systems deployed by regulated entities?

Part 11 requirements do not specify any particular method for implementing access controls
"Regulated entities must ensure that procedures and processes are in place to safeguard the authenticity, integrity and, when appropriate, confidentiality of electronic records"
"The selection and application of access controls should be based on an appropriately justified and documented risk assessment"
"A record should be maintained of all clinical trial personnel who are authorized to access the electronic system as well as a description of their access privileges. This record should include:

- The date the user is added
- User's rights and permissions
- Any changes to rights and permissions

These records should be available to clinical investigators to ensure trial personnel have been granted appropriate access

Q12 What are FDA's expectations for use of audit trails by regulated entities?

"To ensure the trustworthiness and reliability of electronic records, audit trails must capture electronic record activities including all changes made to the electronic record, the individuals making the changes, and the date and time of the changes and should include the reasons for the changes."

Record changes must not obscure previously recorded information
"Periodic review of the audit trail may be helpful for sponsors to ensure data quality, authenticity and integrity"

The decision to review audit trails should be based on a risk assessment which considers the systems, procedures and controls in place
A risk-based approach should be applied for retaining information on the individuals who accessed the system and the times they did so.

Audit trail format should be searchable and sortable. If that is not possible audit trail files should be retained in static format (e.g. PDF) and clearly correspond to data elements or records (see Q3)

Q13 Should an audit trial record every key stroke?

No. It is not necessary to record every key stroke
And edits to completed fields should be captured in the audit trail

Q14 What controls should be in place to ensure that the electronic system's date and time are correct?

Controls should ensure the data and time are correct and individuals with system administrator roles should be notified if a discrepancy is detected.

"The ability to change the date or time should be limited to authorized individuals with system administrator roles, and any changes to date or time should be documented"
If the clinical investigation spans different time zones the sponsor should indicate the time zone that corresponds to the data and time stamp or indicate that times are recorded as Greenwich Mean Time (GMT)

Q15 What are the requirements and recommendations regarding training of individuals who use electronic systems in clinical investigations?

"Anyone who develops, maintains, or uses electronic systems subject to part 11 must have the education, training and experience necessary to perform their assigned tasks"
"Training should be conducted before an individual uses the system, during the study as needed, and when changes are made to the electronic system that impacts the user"

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?

No
Information Technology Service Providers and Services
Regulated entities can contract with IT service providers for IT services in a clinical investigation (e.g. data hosting, cloud computing software, platform and infrastructure services)
When determining the suitability of the IT service and the IT service provider the following should be considered

- Policies in place to allow the regulated entity to perform oversight of the activities provided
- Processes and procedures in place for validation of specific IT services to be provided (see Q7)
- Ability 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)
- Process in place for data migration, data backup, recovery, contingency plans, and retain records and making them available for FDA inspection
- Access controls for specific IT services used in the clinical investigation including SOPs for granting and revoking access (see Q11)
- Ability to provide secure, computer-generated, time-stamped audit trails of user's actions and changes to data (see Q12)
- Ability to secure and protect the confidentiality of data at rest and in transit
- Processes and procedures in place related to electronic signature controls (see section III.E)
- Relevant experience of the IT service provider

Q17 What should regulated entities include in agreements with IT service providers?

There should be a written agreement with the IT service provider that describes how the IT services will meet requirements.

Before entering into an agreement, the regulated entity should evaluate and select the IT services based on the providers ability to provide data integrity and security safeguards (see section III.C) that are relevant to the service being provided.

"The written agreement should address services that provide data integrity and data security safeguards, such as participant confidentiality, data reliability, and adherence to applicable regulatory requirements.

A plan that ensures the sponsor will have access to data throughout the regulatory retention period should be in place.

Q18 What should regulated entities have available to demonstrate that the IT services are performed in accordance with FDA's regulatory requirements?

Any agreements that define the sponsor's expectations of the IT service provider
Documentation of quality management activities related to the IT service, including documentation of the regulated entity's oversight of the IT services throughout the conduct of the trial

Q19 Would FDA inspect or investigate IT service providers in a clinical investigation?

Yes. The FDA may inspect IT service providers who assume regulatory responsibilities
FDA may also conduct focused inspections of IT service providers to ensure accuracy and reliability of trial records
In all cases sponsors should have access to all study related records maintained by IT service providers
Digital Health Technologies
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 for remote data acquisition can include hardware and/or software
Examples of DHT include but are not limited to wearable sensors, environmental sensors or mobile applications to measure clinical events or characteristics
DHTs can be used to record and transmit data during a clinical trial.
The recommendations in this section apply to DHTs used in a clinical investigation, whether provided by the sponsor or when the participant is using their own DHT and/or other technologies
Note the FDA Guidance Digital Health Technologies for Remote Data Acquisition in Clinical Investigations provides recommends on the use of DHTs including recommendations for ensuring the DHT is fit for purpose
All principles discussed in sections IIIA through C of this guidance apply when DHTs are used to record data in a clinical investigation

Q20 When using DHTs to record data from participants in clinical investigations, how do sponsors identify the data originator?

The sponsor should maintain a list of authorized data originators. This list should be available during an FDA inspection

Q21 How should data attribution be ensured when DHTs are used to record and transmit data in clinical investigations?

Sponsors should ensure that data obtained using DHTs are correctly attributed to the data originator. Approaches may include the use of access controls, participant education, and data monitoring.

For certain DHTs (e.g. wearable sensors) access controls may be difficult to implement.
Sponsors should consider how they will address user authentication and data attribution for these DHTs. This is particularly important if the DHT data will support a clinical endpoint.

Q22 What should be considered during the transfer of the data from a DHT to the durable electronic data repository?

Data and any relevant metadata should be transmitted by a validated process according to the sponsor's pre-specified plan.

Transmission should occur contemporaneously or as soon as possible after data are recorded.

Q23 For inspection purposes, what is the location of the source data recorded by a DHT?

FDA does not intend to inspect individual DHTs for source data verification
For inspection purposes the source data are in the durable electronic data repository (e.g. EDC, cloud-based platform).

Electronic Signatures

"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"

Electronic signatures must contain:
printed name of the signer
the date and time when the signature were executed
the meaning associated with the signature

When an individual executes a series of signings during a period of single, continuous controlled system access, the first signing must be executed using all electronic signature components but repeated (subsequent) signings may be executed using one electronic signature component that is only executable by and designed to be used only by the individual.

Q24 What methods might be used to create valid electronic signatures?

Part 11 specifies criteria for electronic signatures to be trustworthy, reliable and generally equivalent to handwritten signatures . . . but do not specify a particular method to create a valid electronic signature.

Regulated entities using commercial off-the-shelf electronic signature services should ensure these confirm to part 11 requirements. This confirmation can be based on:

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?

No. Signatures drawn with a finger or electronic stylus are considered handwritten signatures.

Q26 How should regulated entities verify the identity of the individual who will be electronically signing records as required in part 11.100(b)?

Part 11 does not specify a particular method for verifying the identity of the individual who will be electronically signing records.

Q27 What requirements must an electronic signature based on biometrics meet to be acceptable?

Electronic signatures based on biometrics must be designed to ensure that they cannot be used by anyone other than their genuine owners.

Biometrics should be uniquely identified with individuals and should not change over time Electronic signatures based on biometrics that meet the requirements under part 11, subpart C are considered trustworthy, reliable, and generally equivalent to handwritten signatures.

Q28 Does FDA certify electronic systems and methods used to obtain electronic records?

No. FDA does not certify electronic systems and methods used to obtain electronic signatures FDA would consider electronic signatures to be trustworthy, reliable and generally equivalent to handwritten signatures if the signature and associated electronic records meet part 11 requirements, regardless of brand or technology.

Q29 Are users of electronic signatures required to submit letters of non-repudiation to FDA to certify that an electronic signature is the legally binding equivalent of a traditional handwritten signature?

Yes. Before or at the same time a person uses in electronic signature in an electronic record required by the FDA, users must submit a letter of non-repudiation to FDA.

Organizations may submit one letter of non-repudiation to cover all electronic signatures used by that organization.

Appendix 2 Reference Related FDA Guidance

Conducting Clinical Trials With Decentralized Elements

September 2024
Provides recommendations for sponsors, investigators, and other interested parties regarding the implementation of decentralized elements in clinical trials. Decentralized elements allow trial-related activities to occur remotely at locations convenient for trial participants.

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

December 2023
Provides recommendations on the use of digital health technologies (DHTs) to acquire data remotely from participants in clinical investigations that evaluate medical products.

Use of Electronic Health Records Data in Clinical Investigations

July 2018
Intended to assist sponsors, clinical investigators, contract research organizations, institutional review boards (IRBs), and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

August 2023
Discusses the applicability of FDA's investigational new drug application (IND) regulations under part 312 (21 CFR part 312) to various clinical study6 designs that utilize RWD. The guidance also clarifies the Agency's expectations concerning clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness and safety of a drug (e.g., as part of a new drug application (NDA) or biologics license application (BLA)) when such studies are not subject to part 312. This guidance focuses primarily on clinical study designs that are non-interventional.

www.acdmglobal.org