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What is 21 CFR Part 11?

Title 21 Code of Federal Regulations governs Food and Drugs. Part 11 is the Food and Drug Administration (FDA) guidelines that sets forth the criteria under which the Agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. This regulation, which applies to all FDA program areas, was intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

 Code of Federal Regulations Title 21

Guidance > Part 11, Electronic Records; Electronic Signatures — Scope and Application

Guidance > General Principles of Software Validation

Guidance > 2007 Guidance for Industry Computerized Systems Used in Clinical Investigations

Electronic Submissions Guidance > Sortable listing of Electronic Submissions Guidances

What does HIPAA/Part 11 validation mean?

Performing a software validation entails documenting that a system operates in an expected and predictable manner. This is done to document the system meets HIPAA/Part 11 requirements. The goal of HIPAA and Part 11 is to give patients control over who can access and use their Protected Health Information (PHI). As PHI is collected and stored by systems like REDCap, it is important to document and test the system to demonstrate control over the data.

The level of documentation created during a validation effort will vary by organization. Validation requires a subjective interpretation of HIPAA/Part 11 guidelines by each organization. Decisions on what documentation to create and what testing to perform are risk-based and each organization must determine their individual comfort level with the amount of documentation vs. how much they wish to verbally explain to an auditor. Typically, the functionality of the system is defined through a set of system requirements (things the system must do). These requirements are then tested to ensure the system operates as expected. What constitues a "requirement" is one the largely subjective aspects of validation. Certainly, vital functions of REDCap such as the collection, storage and exporting of data would be considered requirements. Other functionality may or may not be based on your organization's culture, environment, implementation, etc. For those utilizing LDAP for authentication, that functionality is a requirement. For others, it is not.

Why should I perform a validation of REDCap?

Any healthcare provider, health plan or healthcare clearinghouse is almost certainly considered a "covered entity" and therefore subject to HIPAA/Part 11 guidelines. If you fall into one of those three groups, you should be performing some level of validation. In addition, it is difficult to collect meaningful data that does not contain PHI as even a phone number can be considered PHI.

It is important to note that not much validation is occurring industry-wide at this level. Currently, most investigator-initiated research is stored in Microsoft Excel and Access. REDCap offers access from the Internet, security, activity tracking, backups and centralization. These technical advantages coupled with validation documentation should make the FDA extremely pleased when they arrive for an audit. Consider this when planning your validation effort - an auditor should not say you have documented something incorrectly, just that you either did not document something and/or you did not follow your documented policies/procedures. There is no template

or blueprint for validation. As stated above, what constitutes validation will vary with each organization.

The DTMI approach to validating REDCap

Early in the validation effort, we determined that REDCap can meet some compliance guidelines but may struggle to meet all guidelines. Duke has several fully compliant systems available to researchers (such as Inform and Oracle Clinical) and we decided that in addition to validating REDCap we would place studies in the systems most appropriate for them. Early Phase I and II studies would be entered into REDCap. As they moved into later phases and began approaching submission to the FDA, we would migrate the studies to one of the fully compliant systems.

We utilized a two step, OQ (Operational Qualification)/PQ (Production Qualification) approach to the validation. The OQ covers general system functionality as well as any functionality specific to the DTMI implementation (such as LDAP). The PQ verifies that study parameters for a specific database work as expected (such as calculated fields). An audit of the system would consist of reviewing the OQ documentation plus the PQ for the study being audited. The combination of documentation demonstrates comprehensive control of the system.

The OQ documentation consists of the following:

Validation Plan - Explains what the software is and how we are going validate the system. Includes the what, why, who and how aspects of the system.

System Requirements Specification - Lists the functional requirements of the system. What must the system do.

Implementation Strategy - Describes the approach for implementing the system. This document covers licensing, data migration, impact on other systems, security, customization and error handling.

Installation Qualification - Documents the process of installing the system. Contains the required hardware and software, installation instructions and people involved.

System IQ Test - Documents the steps performed when installing the system into the development and validation environments. Each step is signed and dated and the results are documented.

Requirements Traceability Matrix - This document ties each requirement in the System Requirements Specification to its related system test.

System Tests - These are the tests that verify each system requirement functions as expected.

Problem Reports - Any system test that fails requires a problem report that details the problem, the solution (if applicable) and the action taken.

Deployment IQ Test - Documents the steps performed when installing the system into the production environment. Each step is signed and dated and the results are documented.

Release to Production - This is the official document stating the system is now in production.

The PQ documentation consists of the following:

IQ Plan - Documents the steps required to put a new REDCap database into production. This is a general document and not specific to a single database. Its intended purpose to document how all databases will be entered into REDCap.

IQ Test - Documents the steps taken when a new REDCap database is entered into production. This document is specific to a single database and verifies all fields performed as expected. A

new IQ Test will be generated for each database entered into REDCap.

Is REDCap 21 CFR Part 11 compliant?

REDCap has the features necessary to serve as the database component of a 21 CFR Part 11 compliant study. However, the software must be placed in an environment with servers, security, personnel, policies, procedures, training, validation and documentation meeting the requirements of Part 11 and the predicate rules for the underlying legislation. An FDA auditor will review all of this documentation to determine **AT THE PROJECT LEVEL** if a study is compliant.

The REDCap Part 11 Compliant Project's goal is to develop a REDCap "Compatibility" Module and help created supporting documentation and templates. At best, REDCap can offer an application containing the required technical requirements of a compliant system – the rest is up to the institution.

When do I need to be 21 CFR Part 11 Compliant?

According to FDA's 2007 Guidance for Industry Computerized Systems Used in Clinical Investigations:

If you are conducting a clinical trial and using computerized systems that contain any data that are relied on by an applicant in support of a marketing application, including computerized laboratory information management systems that capture analytical results of tests conducted during a clinical trial.

- Applies to computerized systems that create source documents (electronic records) that satisfy the requirements in 21 CFR 312.62(b) and 812.140(b), such as case histories.

- Applies to recorded source data transmitted from automated instruments directly to a computerized system (e.g., data from a chemistry autoanalyser or a Holter monitor to a laboratory information system).

- Applies to when source documentation is created in hardcopy and later entered into a computerized system, recorded by direct entry into a computerized system, or automatically recorded by a computerized system (e.g., an ECG reading).

-**Does not apply** to paper records submitted electronically (scanned, faxed copies)

What data is submitted to the FDA?

Applicants typically submit study reports, which describe the study protocol, the data collected, the analyses performed, the results of those analyses, and the conclusions of the study. Also accompanying the study reports are the case report forms (CRFs), and the study data as case report tabulations (CRTs) and analysis datasets.

CRFs are the forms used by the clinical investigator to document the collected data. The CRTs are aggregate (i.e., data from multiple subjects grouped together) listings of all the data collected on the case report forms.

CRFs and CRTs allow the Agency to perform an independent analysis of the study data. FDA may perform its own independent analyses of study data to assess the effectiveness and safety of investigational products. Analysis datasets are a subset of all data collected in the study and are the critical dataset to support the primary study analyses contained in the study report.

What are clinical trials?

- Biomedical or health-related research studies in human beings that follow a pre-defined protocol.

- Register trials at: http://www.clinicaltrials.gov

Can I use REDCap for studies requiring 21 CFR Part 11 compliance?

Each institution must determine their compliance status.

When will REDCap be 21 CFR Part 11 compliant?

The FDA does not provide an overarching determination of compliance. Even after a successful FDA audit of a study using REDCap, it will only imply that for that specific study, REDCap was *used in compliance* with 21 CFR Part 11. This has yet to happen across the REDCap Consortium.

Can projects that do not require Part 11 compliance use REDCap's E-Sig feature?

The E-Sig specifications were based on the 21 CFR Part 11 federal regulations requirements. If you use the E-Sigs for another purpose, it is unsure how you could enforce it as a "legal" and binding signature. An undesirable action could be that someone denies they signed off on any of the forms, claiming "it wasn't me". Then there's no accountability or recourse you can take.

This is why for Part 11, there's more than just the technical controls in play - there's all the SOPs involved with authentication and end-user agreements.

Financial institutions fall under the Federal ESIGN Act and Gramm- Leach-Bliley (GLBA) Act. It's recommended to first look to see under what context you require e-sigs and then, if applicable, find the corresponding regulation.