Electronic Signatures for Clinical Trial Documents

Ensuring 21 CFR Part 11 Compliance

A White Paper

8 August 2020

Advanced Contract Research Organization

Contents

1. Introduction

With an increase in the use of technology in the 1990s and early 2000s, the FDA worked to establish regulations and guidelines to enable increased use of electronic documentation while continuing to ensure the security and accuracy of data and regulatory documents including the use of electronic signatures. In addition, with the recent challenges of the COVID-19 pandemic, the use of electronic signatures is increasing as research personnel work remotely and handling printed documents for hand written signatures has become logistically difficult as well as less safe due to potential transmission of the virus. Sponsors and Investigators of FDA regulated research must work to ensure compliance with FDA regulations as business processes change.

2. Background and Overview

In 1997 the FDA issued 21 CFR Part 11 regulations, providing the requirements for electronic records including the use of electronic signatures, making them equivalent to hand-written signatures enabling a wider use of technology in carrying out FDA regulated research. In 2003, the FDA issued a guidance document to assist researchers in understanding the scope and applicability of the regulations in Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application.

According to the guidance document, Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations and to electronic records submitted to the Agency. For sponsors and investigators conducting FDA regulated research and using electronic signatures, this means that all documents used for the purpose of the research must meet the requirements of the regulation.

The table below shows some of the most commonly referenced records requirements set forth in Agency regulations that affect Sponsor's and Investigators of FDA regulated research:

Regulation/Guidance	Description	Types of Records
21 FR 820	Quality Systems Regulations	Medical Device manufacturing records
21 CFR 312.62	Investigator Record Keeping and Record Retention	Disposition of IP, Case histories including CRFs and supporting documents, ICFs, medical records, progress notes
21 CFR 312.64	Investigator Reports	Progress reports, safety reports, final reports, financial disclosures
21 CFR 312.66	Investigator Reports to IRB	UPIRTSO reports, progress reports
21 CFR 50.27	Documentation of Informed Consent	Signed ICFs and short forms
21 CFR 312 Subpart B	IND	IND requirements such as Protocol, Protocol amendments, CMC information, information amendments, safety reports, annual reports, withdrawal of IND

Other documents and records collected during the course of research and filed in the Sponsor's Trial Master File demonstrate that the trial was conducted following principles of Good Clinical

Practice (GCP) and are auditable by the FDA. Although the GCP guidance adopted by the FDA, ICH E6, as well as other instrumental guidance documents are technically not regulations, they are used extensively by FDA for inspections and assessment of compliance. Alternative approaches to the FDA recommendations are acceptable but many guidance documents reference the regulations that are being interpreted and those regulations are enforceable by FDA. Sponsors and Investigators are taking on risk if research is conducted without following the FDA's guidance on critical topics and processes.

One of the principles of GCP is the filing of essential trial related documents by both the Investigator and the Sponsor. The types of documents that need to be filed are outlined in section 8 of the ICH E6 document. The Drug Information Associated (DIA) created a TMF reference model that drills down into even more detail, creating a best practice document with very specific information on what documents should be on file and recommendations for file structure. Many of the TMF documents require or are recommended to have signatures. If electronic signatures are used for TMF documents the 21 CFR Part 11 requirements should be utilized since these are the documents that are used to re-create the conduct of the trial, contribute to the data and FDA submission, and many are covered under the various records regulations mentioned previously.

The following are common TMF documents that should be signed and should meet the FDA requirements for electronic signature when that is utilized:

- Trial Plans (Quality, Clinical Monitoring, Data Management, Statistical Analysis, Risck Management, etc.)
- SOPs being used in the trial
- Audit Certificate(s)
- TORO
- Protocol and Amendments
- Financial Disclosures
- Trial-related Memos, Letters, Forms, and File Notes
- FDA Forms (1571, 1572)
- Agreements
- Monitoring Reports
- CVs
- Delegation Logs
- Approved Blank Case Reports Forms (paper studies) or Approved Mock eCRFs (EDC Studies

3. Enforcement Examples

There multiple examples from the past 10 years of FDA warning letters to companies referencing 21 CFR Part 11 requirement compliance issues. Some findings include, lack of validation of electronic systems, procedural issues for back up data, change control process issues, improper and inadequate security for user names and passwords, lack of audit trails, and computer validation issues. In their warning letters the FDA questions the reliability of the

data used for development decision-making and failure to maintain the integrity of records (Allevant, 2011).

Though more rare, there have been warning letters with citations specific to electronic signatures. One warning letter sent to EMcision LTD in November of 2014 cited a failure to follow the company's document management procedures when signing numerous procedure documents electronically. The company's response that approved electronic signature systems were not in place at the company was inadequate to the Agency. As trends for remote work and increasing reliance on electronic signatures continue, it is reasonable to assume that inspections of electronically signed documents could result in increased scrutiny of the electronic signature processes.

4. Solutions

There are several commercially available solutions available for electronic signatures that meet the FDA requirements for electronic signatures. Below are a few examples of available products.

Company Name	Product	Comments
Adobe	Adobe Pro DC	Requires set up in preferences for the ability to show the "reason for signature" and staff must ensure that they enter the reason from a drop-down upon signing
DocuSign	DocuSign Life Sciences Module	Must contact the company for pricing and details. Standard DocuSign software does not meet the Part 11 requirements
SIGNiX	PharmaDoX	Takes the digital signature that is used by default at SIGNiX and places it in a 21 CFR Part 11-compliant workflow. Automatically logs all necessary information required by the FDA as a natural part of the signing process

5. Summary

With the increase in the use of technology in clinical research as well as the change in business processes due the current pandemic, it is important for Sponsors and Investigators of FDA regulated research to determine how they will ensure compliance with electronic signature requirements in the current environment. Electronic signatures created without the proper controls and documentation in place can result in negative findings during an FDA inspection and a determination by the agency that data submitted by the company or institution are unreliable or untrustworthy. Ensuring compliance in all areas of FDA regulations will advance the overall reputation and credibility of the institution when submitting data and other documents to the FDA and during inspections by FDA representatives.

6. References

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