Guidance on Use of Electronic Signatures in Research and Title 21 CFR Part 11 Compliance

Purpose of the document: This document explains several options for the use of electronic signatures in research at Penn Medicine and the relationship to Title 21 CFR Part 11[1] FDA regulation. This document's audience is research and clinical staff engaged in human subject research who may be requested to use electronic signatures by their sponsors. This document covers certain uses of e-signatures for research trial related documents and systems as described below, however it does not cover the use of electronic signatures related to contracting, business administration, grant submission (PennERA), or the effort reporting system (ERS).

Stakeholders of this guidance document: Perelman School of Medicine investigators and research staff, the Office of Clinical Research (OCR), Penn Institutional Review Board (IRB), Penn Medicine Corporate Information Services (also Digital Academic Research Transformation, DART).

Background: Title 21 CFR Part 11 is the part of the Code of Federal Regulations that establishes the United States Food and Drug Administration (FDA) regulations on electronic records and electronic signatures (ERES). Part 11, as it is commonly called, defines the criteria under which electronic records and e-signatures are considered trustworthy, reliable, and equivalent to paper records (Part 11.1 (a)). It requires the use of audits, system validations, audit trails, electronic signatures, and documentation for software and systems involved in processing electronic data.[2] Not all studies require Part 11 compliance- generally studies under the jurisdiction of the FDA (IND/IDE studies) require full Part 11 compliance. In general, sponsors and other regulated entities should have electronic systems validated if those systems process critical records (e.g., records containing laboratory and study endpoint data, information on serious adverse events and study participant deaths, information on drug and device accountability and administration) that are submitted to FDA. The extent of validation should be tailored to the nature of the system and its intended use.

What is an electronic signature (e-signature): E-signatures are the legally binding equivalent to an individual's handwritten signature (Part 11.3(b)(7)). The FDA does not specify any methods for creating valid e-signatures, and permits methods such as ID cards, biometrics, and username/password combinations. An e-signature is not necessarily a visual representation of a handwritten signature and can be an individual specific number series associated with a username and password. For this guidance, we are addressing the use of electronic signatures to sign off on certain research related and clinical research essential documents.

[1] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11
[2] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

Current e-signature use in research related departments:

Department/System/ Application	Type of signature used	Compliance with Titles 21 CFR Part 11	Note
Adobe	Place e-signature on a location on a document page	Variable depending on application	Adobe Sign has Part 11 compliant package available
Docusign	Sign envelope for a document	Can be compliant	DocuSign has Part 11 package available
IRB	Uses Adobe Acrobat to electronically sign off on documents	Partial	Complies with FDA 21 CFR 11.5, 11.7 and Subpart C[3]
Penn Medicine Electronic Health Records (EHRs)- PennChart/EPIC	EHRs contain digital signatures	Partial	EHRs at Penn Medicine are not designed to meet FDA 21 CFR 11 criteria for electronic signatures via third party authentication[4]
PennCTMS Clinical Trial Management System	PennCTMS uses a 4 digit e-signature	System is compliant	Use is constrained to patient management and tracking, some electronic data capture via forms
REDCap	Can be used for electronic consent or subject completed outcome data collection	Not validated	Does not meet Part 11 compliance, can be used for e-consent for signatures that do not need to meet full part 11
Veeva applications (e.g. SiteVault, eTMF)	Uses PennKey single sign on for document sign off	System is compliant	User e-signatures are appended as a separate signature page

Examples of e-signature use in research:

- To authorize updates, exchange and approve of training records and SOPS from different sites
- For remote approval when licensed medical practitioners are not on site to review documentation of adverse events, and
- To confirm authorship in electronic data capture

[3] http://www.upenn.edu/IRB/sites/default/files/21CFR11%20Statement%20of%20Compliance_2016Update.pdf
[4] http://www.med.upenn.edu/ocrobjects/prod/attach/PennMed_Electronic_Health_Records.pdf

- To verify inventory and authorize dispensing of investigational product

E-signatures can also be used in regulatory compliance and allow electronic tracking for audit purposes including time stamping, and identity verification. Use of e-signatures for consenting depends on the protocol and whether the study requires Part 11 compliance. To collect an e-signature remotely, investigators have several options (Part 11 compliance varies):

- Use a digital consent form or platform that provides the consent form and captures an e-signature at the end (e.g., REDCap for studies that do not require Part 11 compliance)
- Use an e-consent file containing fillable fields (e.g., PDF) with e-signature, sending to and from the participant through secure email or file transfer
- Collect a picture or image of the entire paper consent form with all pages and signed signature page through secure email or file transfer
- Collect a scanned signed copy of the whole consent form through secure email or file transfer. Scans can be created with a document scanner or a phone application (e.g., Adobe Scan).

Note: E signatures are only one piece of the electronic signature process. They may be combined with an in-person consent discussion or the consent process may take place via an electronic/ telecommunication platform. For more information see OCR's Telemedicine Guidance.

To determine whether you may use e-signatures for your documentation, check with your study sponsor or sponsor-investigator to confirm the protocol's compliance requirements and if documents must be wholly Part 11 compliant. Some sponsors may request or require wet ink signatures over e-signatures, or the reverse. If an e-signature does not need to be completely Part 11 compliant, Adobe Acrobat[5] can be used to create a password protected, time stamped electronic signature. Depending on the document type, other systems such as REDCap or Veeva may be appropriate.

Application options with built in e-signatures: REDCap is HIPAA compliant (not Part 11 compliant) and recommended for consenting with e-signature for non-IND/IDE studies. Penn Medicine's Clinical Trials Management System, PennCTMS/Velos, uses Part 11 compliant e-signatures, however it cannot be used to author documents or consent. PennCTMS is best used for e-signatures associated with document review, e.g. adverse event review, Case Report Form (CRF) review or sign off. PennChart (EPIC) is not Part 11 compliant, but contains an e-signature component and can be used for research consenting. PennVault applications (such as SiteVault, electronic Trial Master File, QualityDocs) also use Part 11 compliant e-signatures to approve documents.

[5] https://helpx.adobe.com/acrobat/11/using/signing-pdfs.html

Application options with stand-alone e-signatures: The University of Pennsylvania offers access to DocuSign (Part 11 compliant)[6] with a cost per envelope, click the link for more information on Part 11 compliance. Adobe[7] also offers an e-signature application with full Technical Controls for Part 11 compliance, priced on a monthly subscription model.

OCR encourages study teams to discuss with their study sponsors before operationalizing e-signatures. When engaging with vendors or considering purchasing technology outside PSOM licenses, always contact your DART Service Information Officer (SIO) via email to dart_sio@pennmedicine.upenn.edu . Faculty sponsors requiring assistance regarding systems and application requirements for FDA submissions should contact OCR's Sponsor Support Unit via email to psom-ind-ide@pobox.upenn.edu .

Staff compliance for e-signatures: Full Part 11 compliance goes beyond the software and electronic system implemented and requires that staff be trained in and follow the appropriate study specific standard operating procedures. Training with procedures should be documented. A password must be entered for each e-signature, signatures should not automatically populate. Training should include that passwords and login information must not be shared between staff, and that they are accountable for electronic signatures (e.g., Staff should sign a document indicating "I understand that electronic signatures are legally binding and have the same meaning as handwritten signatures.") Primary investigators, sub-investigators, and all research staff cannot delegate signing documents with their electronic signature to another staff member. If the system or application being used for e-signature undergoes an upgrade or change, verification of no impact to e-signature and retraining may be required. The level of change control and re-training should be commensurate with the risks to study data.

References:

FDA CFR Part 11, Electronic Records; Electronic Signatures at the Electronic Code of Federal Regulations
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11
Federal guidance:

- Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 -- Questions and Answers (June 2017) Draft Guidance
  https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm563785.pdf
- 21 CFR Part 11 Electronic Records and Signatures (August 2003) Final Guidance
  http://www.fda.gov/regulatoryinformation/guidances/ucm125067.htm

This guidance was drafted by the Office of Clinical Research. Please direct questions to the Office of Clinical Research at psom-ocr@pobox.upenn.edu or 215-662-4484.

[6] https://support.docusign.com/en/guides/cdse-admin-guide-part-11-compliance

[7] https://helpx.adobe.com/sign/using/21-cfr-validation-pack.html