Electronic Signatures	CR-402
Clinical Research Standard Practices	**Effective Date:** December 2023

SCOPE AND PURPOSE The document is applicable to the following roles within Penn State College of Medicine and all Penn State Health entities engaged in clinical research:

Roles:

X	Principal Investigators	X	Regulatory Specialists
X	Sub-Investigators	X	Key Study Ancillary Personnel
X	Study Coordinators/Associates	X	Financial Analyst/Research Accountants
X	Data Specialists	X	Central Research Office Personnel

The purpose of this document is to provide guidance for the use of electronic signatures for clinical research documents.

This SOP may be shared with Sponsors and/or CROs upon request.

POLICY AND PROCEDURE STATEMENTS

1. General standards
    a. Documents deemed "essential" by International Conference on Harmonization (ICH) Good Clinical Practice (GCP) or are regulated by the United States Food and Drug Administration (FDA will be electronically signed using a 21 CFR 11 (henceforth "Part 11") compliant system. Such essential documents are those that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Such documents include, but not limited to:
        i. Protocol signature pages
        ii. Acknowledgements of receipt of Investigator Brochures and Instructions for Use
        iii. Initial interpretation of data
        iv. Note to File regarding the interpretation of data.
    b. Documents not deemed "essential" by ICH GCP, not regulated by the FDA, or are internal only may be electronically signed using a non-Part 11 compliant system; however, use a Part 11 compliant system is encouraged. Such documents include, but not limited to:
        i. Notes to File
        ii. Principal Investigator (PI) oversight of central/core lab reports
        iii. PI oversight of local laboratory and testing reports
        iv. PI oversight and acknowledgment of monitoring reports
        v. PI oversight of sponsor-generated safety reports
        vi. Sponsor/Contract Research Organization (CRO) administrative forms
        vii. Study team acknowledgement of review of key communication, newsletters, and similar

viii. Training logs

c. Tampering or falsifying electronic signed documentation or using any electronic signature account other than the account owner are in direct violation of federal regulation and institutional standards and will be reported accordingly.
d. Electronically signed documents submitted to the FDA must be Part 11 compliant.
    i. To meet this requirement, all individuals shall complete a Certification of Electronic Signature Form prior to or at the time of using electronic signatures.
    ii. Persons using electronic signatures shall, prior to or at the time of such use, certify to the FDA that the electronic signatures in their system are intended to be the legally binding equivalent of traditional handwritten signatures.
    iii. Institutional signatories shall provide a non-repudiation letter to the FDA prior to the use of electronic signatures on any clinical trial document attesting to the fact that their electronic signatures are legally binding equivalents of their traditional hand-written signatures.
        1. The institutional signatories are:
            a. Assistant Vice President for Finance and Business and Controller, College of Medicine
            b. Senior VP and Chief Financial Officer, Penn State Health
        2. The Clinical Trials Office will maintain copies of any non-repudiation letters sent to the FDA. in the Investigative Site Files
        3. The non-repudiation letter shall be updated whenever there is a change in an institutional signatory.

2. Certification of Electronic Signature Form Signature Logs
    a. The completion and maintenance of the Certification of Electronic Signature Forms for any clinical research study shall be the equivalent of a signature log for any clinical research studies where only wet-ink signatures are collected on study documents.
    b. The purpose of a signature log is to have a record of the signature sample of every individual involved in study-related activity. Therefore, Certification of Electronic Signature forms shall also serve as the wet-ink signature sample of every individual involved in study-related activity should any wet-ink signature be collected on any study documents.
    c. An individual Certification of Electronic Signature Form should be maintained for each team member who is involved in a study.
    d. The Certification of Electronic Signature Form will include:
        i. Printed name
        ii. Signature
        iii. Initials
        iv. Date when the signature log was completed.
    e. The Clinical Trials Office (CTO) Director or designee will initiate the Certification of Electronic Signature Form with each new user.
    f. Each Team member should provide a complete handwritten copy of the Certification of Electronic Signature Form to the CTO Director or designee.
    g. Each completed Certification of Electronic Signature Form will be uploaded and stored in the Florence Electronic Trial Master File (eTMF) or Electronic Investigative Site File (eISF) by the CTO Director or designee.

h. In case of a name change for a Team member, a new Certification of Electronic Signature Form must be created and uploaded to Florence eTMF/eISF.

3. Electronic Signatures via DocuSign
    a. This section applies to all documents and clinical research studies and trials where DocuSign is utilized and where electronic signatures and handwritten signatures executed to electronic documents are intended to be equivalent to paper records and handwritten signatures.
    b. Requesting Electronic Signatures
        i. Using DocuSign, the document will be uploaded and sent to the identified individual(s) for signature.
            1. If the document or part of the document needing signature is an FDA regulated or best practice document, then a Part 11 compliant electronic envelope must be used.
            2. If all the documents are for internal use and do not contain any FDA regulated documents using a non-Part 11 electronic envelope is acceptable
            3. The individual or party requesting document signature (sender) will review the document for completeness and accuracy to the best of their ability within the scope of their role.
                a. Some parts of the document can be completed by others once uploaded to DocuSign, but once any signature is placed on any document or part of any document within an envelope, the content of the document(s) must not be altered. The document after signature is considered source data.
        ii. Only official email addresses for signatories shall be used to verify the identity of the individual. An email address is deemed official if the domain name is a recognizable entity (e.g., pennstatehealt.psu.edu, psu.edu, fda.gov, etc.) Use of personal emails (e.g., Gmail, AOL, internet service providers, etc.) is not permitted.
    c. Retrieve, Review/Sign a Document
        i. An email will be sent stating that a document is ready for review and signature.
            1. The email will contain a link that will take the signer directly to the document within the DocuSign system.
            2. The signatory will need to log in with their DocuSign credentials before signing can be completed.
        ii. The signatory will review the documentation and sign in the designated locations.
        iii. After all signatures are affixed, the DocuSign system will ask the signatory to press finish which will automatically send out a notification that the tasks are complete.
        iv. A copy of all documents the recipient has signed, and the final completed document(s) are stored in DocuSign for future retrieval or review.
    d. Filing Electronic Signature Documents
        i. Once electronic signatures have been affixed, DocuSign will provide a notification of completion.

ii. Electronically signed documents will be downloaded along with the completion certificate and filed in the appropriate binder, electronic folder, and/or chart. The completion certificate links the recipient to their Electronic Record and Signature Consent Disclosure which makes the e-signature Part 11 compliant.
    1. All original documentation without signature can be considered superseded; the exception is if the original documentation includes source data or contains other signatures.
iii. If an electronically signed document contains a wet ink signature(s), the wet ink document will be maintained with the electronically signed document.
iv. Documentation with electronic signature should be maintained via PDF in the electronic binder or server, and a hard copy should be maintained in the regulatory binder (as applicable)

4. Electronic Signatures via Florence eBinders
    a. This section applies to all documents and clinical research studies and trials where eTMF/eISF is utilized and where electronic signatures and handwritten signatures executed to electronic documents are intended to be equivalent to paper records and handwritten signatures.
    b. Users are responsible for reviewing their accounts for pending signature requests on a regular basis.
    c. Electronic signatures may be used for all documents stored in Florence eTMF/eISF, except:
        i. Clinical research agreements (e.g., clinical trial agreements, confidentially/non-disclosure agreements, subaward agreements, etc.)
        ii. Any documents containing original or copied wet-ink signature
    d. Signatures only apply to the version of the document signed. Any updates to a version of the document do not carry over signatures from the previous version. Any updates which require review, acknowledgment, and/or approval must be signed by the appropriate Users.
    e. Documents can be signed in Florence by Stamp or Addendum signatures. Use of the Addendum (invisible) signature option and the Stamp (visible) signature option are seen as equivalent and can be utilized on all electronic documents interchangeably as both signature types maintain the details required by Part 11.
    f. Signature requests can be made by individuals with the appropriate permission and access to do so within Florence eISF.
    g. Signing Documents
        i. The individual signing the document reviews the document and the requested reason for their signature in Florence eTMF/eISF.
        ii. If the individual agrees, the username (authorized organization email address) and password (or signing PIN) are entered, and the system confirms that they match the User's verified secure credentials.
        iii. The signature addendum page and audit trail for the document are updated to reflect the new electronic signature, its reason/meaning, and the date and time of execution.

RELATED POLICIES AND REFERENCES

Code of Federal Regulations: Electronic Records; Electronic Signatures (21 CFR 11)

International Conference on Harmonization Good Clinical Practice E6(R2)

Florence Compliance Team Key Training Resources: FDA (Part 11 Predicate Rules) ICH, GCP EU/UK GDPR and More! (https://florencehealthcare.zendesk.com/hc/en-us/articles/360048969714)

Penn State University Policy: Contracts and Leases (FN11)

Penn State Health Policy: Signature Authority Policy (PSH L-01)

APPROVALS

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HISTORY OF REVIEWS AND REVISIONS

October 2023	
Scope and Purpose, Roles	Removed list of entities. Updated "Financial Analyst/**Research Accountants**". Added "Regulatory Specialists" and "Central Research Office Personnel." Notation made that this SOP may be shared with Sponsors and/or CROs upon request.
Policy and Procedure Statements	Restructured section. Removed use of certificate-based electronic signatures as an acceptable method. Added Florence eBinders as an acceptable method for obtaining electronic signatures. Updated references.
Related Policies and References	Updated reference for Florence. Updated references for signatory authority.
History of Reviews and Revisions	Section added.