Documentation and Document Management Module
Part 2: Regulatory File

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Agenda

- Define essential documents
- Purpose of the regulatory file
- Types of essential documents
- Centralizing essential documents
- Creating an e-regulatory file

Essential Documents

Documents that demonstrate the compliance of the investigator, sponsor, and monitor with the standards of good clinical practice (GCP) and with all applicable regulatory requirements.

Guidance Documents

- ICH Good Clinical Practice E6 4.9.4
- ICH Good Clinical Practice E6 Section 8

Regulatory Binder

- Organizes essential documents
- Allows research team members to reference information
- Allows easy access to essential documents by trial monitor, auditor, IRB, or regulatory authorities for review/audit purposes

Maintenance of the Regulatory Binder

- Principal Investigator is ultimately responsible for maintenance of regulatory files

- This task is often delegated to other members of the research team

Regulatory Binder Formats

- Various formats are acceptable
- Needs to be organized in a manner that allows specific documents to be found easily
- Important rule of thumb with filing is "consistency"
- Can be paper or saved in a secure word file

Protocol Versions & Protocol Information

Title of Essential Document	Purpose
Protocol & Amendments	To document revisions of trial related documents that take effect during trial.

Investigator & Institution Information

Title of Essential Document	Purpose
FDA form 1572 or investigator agreement	To document the investigator's agreement to conduct the study according to the protocol and GCP.
Current Curriculum Vitae (CV) and copy of medical license	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.
Training Certificates	To document that there is adequate training for all staff participating in the conduct of the study.
Delegation of Authority Log and Signature Form	To demonstrate which study-related tasks the Principal Investigator (PI) has delegated to others. To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.
Financial Disclosure/ Certification Statements	To document that the investigators are compliant with FDA regulations 21 CRF312.64 (d).

Investigator Brochure/ Device Manual

Title of Essential Document	Purpose
Investigator's Brochure (IB) (all versions)	To document that relevant and current scientific information for investigational product has been provided to the investigator in a timely manner.

Approved ICD and Information given to Subjects

Title of Essential Document	Purpose
Informed Consent Documents (all versions)	To document the informed consent.
Advertisements, Recruitment and Patient Education Materials*	To document that subject will be given appropriate written information to support their ability to give fully informed consent. To document that recruitment measures are appropriate and not coercive.
Insurance statement (where required)*	To document that compensation to subject(s) for trial-related injury will be available

IRB Documentation

Title of Essential Document	Purpose
Federal Wide Assurance Number & Expiration date	To document that the institution is registered with the Office of Human Research Protections (OHRP).
IRB Membership Roster	To document that the IRB is compliant with GCP
IRB approvals and correspondence including: initial review, continuing review, advertisements, subject compensation, and other reporting requirements (e.g., unanticipated Problems, protocol deviations and non-compliance).	To document that the trial has been subject to IRB review and given approval. To identify the version number and date of the documents.

Safety Information

Title of Essential Document	Purpose
Copy of Serious Adverse Event (SAE) reports sent to Sponsor	To document that the sponsor was notified of all SAEs and related reports.
IND safety reports	To document that the sponsor informed the investigator of new safety data (e.g., unexpected SAEs related to the product).
Safety and Data Monitoring Committee Reports and Correspondence	To document compliance and actions related to safety monitoring.

Other Regulatory Authority Documentation

Title of Essential Document	Purpose
Correspondence with Regulatory authorizes [e.g., FDA, Radiation Safety Committee, Office of Biotechnology Activities (OBA), Institutional Biosafety Committee (IBC)] regarding safety information (if applicable)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).

Clinical Trial Material Documentation

Title of Essential Document	Purpose
Instructions and Shipping Records of Clinical Trial Material (CTM) and Trial-related Materials*	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials (if not in protocol). To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.
Samples of labels attached to investigational product containers (if applicable)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects.
CTM Dispensing/Accountability Records	To document that investigational product(s) have been used according to the protocol.
Documentation of CTM destruction if performed at site.	To document destruction of unused investigational products by sponsor or at site.

Biological Samples Documentation

Title of Essential Document	Purpose
Record of retained body fluids/tissue samples including transmittal forms and other correspondence (if applicable)	To document location and identification of retained samples if assays need to be repeated.

Laboratory Documentation

Title of Essential Document	Purpose
Laboratory certification and/or accreditation including updates (e.g., College of American Pathologists (CAP), or Clinical Laboratory Improvement Amendment Accreditation (CLIA)]	To document the competence of the facility performing protocol specific tests and support reliability of the results.
Laboratory Normal Reference Ranges including updates	To document normal values for lab tests to be performed for the clinical trial.

Subject Accountability Records

Title of Essential Document	Purpose
Subject Screening and Enrollment logs	To document identification of subjects who entered pre-trial screening and those then that were enrolled.
Subject Identification Code List	To permit identification of all subjects enrolled in the trial in case follow-up is required.
Decoding Documentation (for blinded trials)	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment.

Monitoring Activities

Title of Essential Document	Purpose
Site Initiation Visit report	To document that trial procedures were reviewed with the investigator and the investigator's trial staff
Monitoring Log and Reports including close-out visit	To document site visits by, and findings of, the monitor. To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files.
Documentation of CRF Corrections*	To document all changes/additions or corrections made to CRF after initial data were recorded.
Sponsor Correspondence	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting.

General Documentation

Title of Essential Document	Purpose
Notes to File	To provide documentation of unusual events which occur during the course of a clinical trial.

Notes to File

- Document something unusual that happens
  - Incidents that expose issues with procedures, training or other elements important for proper study conduct require more information.
- A good note includes:
  - Date, author and subject of note
  - What happened? (who, what, where, when, how, why)
  - Why is the incident important?
  - What has been or will be done to address this incident?
  - What will be done to prevent or mitigate similar incidents in the future Document location of central files

General Rules for Maintaining Regulatory File

- Maintain subject confidentiality
  - Black out patient names and other personal identifiers
  - Add subject unique ID #
- File contents need to be easily understood by someone who is not familiar with the study
- For binders:
  - Keep in a secure location
  - File documents in reverse chronological order
  - Do not use binders to hold irrelevant papers

Centralization of Files

- If multiple studies have same regulatory documents, it is acceptable to file in one binder
- Place note to file in each study's regulatory binder indicating location of centralized files
- Examples:
  - Laboratory Certifications and Normal Ranges
  - IRB Membership Lists
  - CVs

E-Files

- Server space & security
  - Daily backed up server or on a secure web-based system
- Monitoring visits
  - Electronic file can be downloaded to a secure memory device
- Develop standard nomenclature to save documents

Standard Nomenclature Examples

Document Name(s)	File name
Initial protocol document	Protocol number_initial protocol_ date [MM-DD-YY]
Initial consent document	protocol number_ initial consent_ date [MM-DD-YY]
Continuing IRB review	Protocol number_CR_date [MM-DD-YY}
Investigator Brochure	<Drug Name_ IBversion_date [MM-DD-YY] (date=date of version) (i.e. MDX010_ IBv6.2_ 12-10-09)
IRB approval document	protocol number_ IRB approval memo_ date [MM-DD-YY]
Financial Disclosure	FDA form 3455_ Investigator name_ date [MM-DD-YY]
CV	CV_investigator name_date
IRB membership roster	IRB roster_date [MM-DD-YY]
Unanticipated Problem	Protocol number_ event_ date of event[MM-DD-YY]

Summary

- Management of essential documents is not governed by regulatory agencies but is recommended per GCP guidelines
- Regulatory file collects the essential documents
- Update various logs in a timely manner
- Acceptable to centralize some of the documents
- All regulatory files should be in a secure location and free of PHI
- Consider creating and maintaining an electronic regulatory file