Regulatory Binder

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National Cancer Institute

Introduction

- A regulatory binder or file contains all study-specific information and regulatory documentation. It organizes essential documents, provides easy access to essential documents by the trial monitor, auditor, IRB, or regulatory authorities (e.g., Office for Human Research Protections, FDA) for review/audit purposes, and allows research team members to reference information. Although the regulatory binder is part of the GCP guidelines (GCP E6 Section 8) and not legally binding, it is highly recommended that all intervention trials have a regulatory binder, regardless of sponsorship. For sponsored trials, the sponsor also maintains a mirror image of the site's regulatory binder.

- By the end of this module, the participant will be able to:
  - Describe the purpose of the regulatory binder.
  - List 10 essential documents found in a regulatory binder.
  - Describe the purpose of the screening log, the enrollment log, and the site visit log.
  - Describe when it may be appropriate to centralize essential documents.

What is a Regulatory Binder?

- Binder/File that contains all study-specific information and regulatory documentation

- Terms used synonymously to describe the Regulatory Binder :
  - Study Binder
  - Investigator Binder
  - Administrative Binder
  - Regulatory Files
  - Investigator's Study Files

What is the Purpose of a 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 (e.g. OHRP, FDA) for review/audit purposes

What are 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.

NOTE: The International Conference on Harmonisation (ICH) Guidelines (ICH GCP E6 Section 8) have been adopted by the FDA as guidances, not regulations

Guidance Documents

- ICH Good Clinical Practice E6 4.9.4
  "The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (section 8) and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents."
- ICH Good Clinical Practice E6 Section 8
  - Specifies which documents are considered essential
  - Gives explanation of purpose of documents
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

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

Organization of the Regulatory Binder

- Various formats are acceptable
  - sponsors, branches may have required format
- Needs to be organized in a manner that allows specific documents to be found easily
- Important rule of thumb with filing is “consistency”

Regulatory Binder Contents….

- **Protocol and Amendments**
  - Initial protocol and ALL amendments with documented IRB and sponsor approvals
- **Informed Consent**
  - ALL approved versions
- **Continuing Reviews**
  - Approvals from IRB
  - Study completion/termination report

…. Regulatory Binder Contents….

- **FDA Form 1572 for all IND Trials**
  - ALL versions signed and dated
  - For CTEP studies: One Form 1572 per MD investigator
  - For non-CTEP studies: One Form 1572 per protocol
- **Curricula Vitae**
  - Demonstrates qualifications of ALL investigator and associate investigators
  - Updated copies, should be signed and dated

…. Regulatory Binder Contents….

- **Serious Adverse Events**
  - Copies of reports
  - Documentation of receipt from IRB, sponsor, FDA, OBA, as applicable
- **IND Safety Reports**
  - Copies of reports
  - Documentation of receipt from IRB

…. Regulatory Binder Contents….

- **IRB Correspondence**
  - Regarding approval process of protocol, amendments
    - Submissions, stipulations, responses to stipulations
    - Does not need to be entire package
    - Keep enough documentation to provide a trail of the process
  - Regarding continuing review
    - reminder notices
  - Clarifying or stating an issue regarding conduct of the study

…. Regulatory Binder Contents….

- **IRB Membership Lists**
  - Copy of ALL IRB membership list and any changes throughout the study

- **Subject Identification Code List**
  - Confidential list of the names of all patients with their study Group assigned identification number
  - Maintained only at the site
  - Allows the investigator or institution to quickly identify study patients in the case of an emergency

…. Regulatory Binder Contents….

- **Investigator's Brochure (IB)**
  - ALL versions of the IB and updates
  - Contains scientific information for investigational product
  - For FDA approved agents, file a copy of the package insert
- **Recruitment advertisements/letters**
  - With documented IRB and sponsor approvals

…. Regulatory Binder Contents….

- **Sponsor Correspondence**
  - Pre-study correspondence as appropriate
  - Details processes and procedures for study conduct
  - Phone logs
  - Site visit letters/summaries

- **Other Correspondence**
  - Any miscellaneous protocol-related correspondence

…. Regulatory Binder Contents….

- **Laboratory Certification**
  - All copies of CLIA certifications for all labs submitting subject results for purpose of the study
  - Need to have valid certifications filed as long as the study is open

- **Laboratory Normal Ranges**
  - Copy of normal ranges for all labs/tests included in protocol
  - If using results for a specific patient as the reference ranges, blacken out all patient specific identifiers, copy and then place in binder

…. Regulatory Binder Contents….

- **Subject Enrollment Log**
  - Log to document chronological enrollment of subjects
- **Subject Screening Log**
  - Log to document patients who entered pre-trial screening period
  - Should document why potential subjects were not included in study
- **Site Visit Log**
  - Log in which monitors will document their visits
  - Site staff will have place to initial/verify that monitor was present on specific dates
  - For consecutive days, each day is entered separately

…. Regulatory Binder Contents….

- **Training Records/Certificates/Inservices**
  - PI should ensure that there is adequate training for all staff participating in the conduct of the study.
  - Keep evidence of training such as:
    - Copy of human research training certification for all study staff
    - Additional training certification of study staff (e.g., chemo certificaiton, phlebotomy, vital signs, etc.)
    - Sign-in sheets/copies of inservices conducted on a specific study
- **Delegation of Authority Log/Signature List**
  - PIs are allowed to delegate certain study-related tasks to others.
  - List of all individuals (including signature and initials) for all persons that are delegated study related activities by the PI.
    - See the CCR Delegation of Authority Log (Form 28) for types of activities that may be delegated.
  - Update this log in a timely manner as new personnel are added and/or study roles change.

…. Regulatory Binder Contents….

- **Pharmaceutical Information**
  - Drug accountability including shipping and dispensing records
  - Sample of labels attached to investigational product containers
  - Decoding procedures (if not detailed in protocol)
  - Documentation may be kept in the pharmacy binder and a copy in the Regulatory Binder

…. Regulatory Binder Contents

- **Blank Set of Case Report Forms**
- **Record of Retained Tissue or Fluid Samples**
- **Notes to File**

Notes to File…

- When something unusual happens in a clinical study, it is common to document the incident with a note to file in the regulatory binder or other study files.
- Incidents can include:
  - decisions made
  - instructions from the study sponsor
  - problems experienced
  - other matters that are important to remember if one is to understand what happened during the study
- The question to ask when writing a note is: “What are the chances that a data query, site monitor, auditor or inspector will ask a question and find this note useful in understanding what happened in the study?”

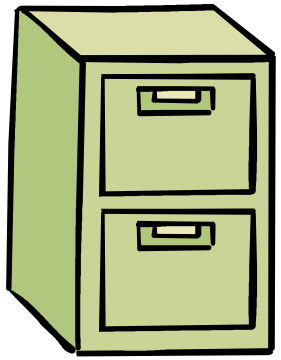
…Notes to File

- Incidents that expose issues with procedures, training or other elements important for proper study conduct require more information. A good note to file 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?

General Rules for Maintaining Regulatory Binder…

- Make sure patient confidentiality is maintained
- Black out patient names and use subject numbers in reports (e.g. expedited adverse event reports, lab reference ranges)
- Binder contents/organization need to be easily understood by someone who is not familiar with the study

…General Rules for Maintaining Regulatory Binder



- Keep binders in a secure location
  - Preferably locked cabinet
  - At a minimum locked office
- File documents in reverse chronological order
- Do not use binders to hold irrelevant papers (i.e. post-it notes to yourself)

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
  - CTEP 1572s

Helpful Hints

- It's better to file documents into regulatory binder as soon as they are received
- Loose documents can fall out of the binder and get misplaced
- Be careful to file documents into the correct study's binder
- Keep in mind the purpose of the binder: to document compliance with GCP and regulatory requirements

Resource

- ICH GCP Guidelines (See section 8 "*Essential Documents for the Conduct of a Clinical Trial*")
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

Evaluation

Please complete the evaluation form and fax to Elizabeth Ness at 301-496-9020.

For questions, please contact Elizabeth Ness
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