Research Regulatory Binder

INTRODUCTION

A regulatory binder is a binder or file that contains all essential study-specific information and regulatory documentation. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. These documents the ones which are typically audited by sponsor monitors and inspected by regulatory authorities as part of the process to confirm validity of the trial conduct and integrity of the data collected. It organizes essential documents, provides easy access to essential documents by a trial monitor, auditor, IRB, and/or regulatory authorities (e.g., Office of Human Research Protections, FDA) for review/audit purposes, and allows research team members to reference information. Although the regulatory binder is part of Good Clinical Practice (GCP) guidelines (CCP 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.

Other Terms used to describe the Regulatory Binder

- Study Binder
- Investigator Binder
- Administrative Binder
- Regulatory Binder/Files
- Investigator's Study Files

PURPOSE OF A REGULATORY BINDER

The purpose of a Regulatory Binder is to organize all of the essential documents into one location to allow easy access to essential documents by a trial monitor, study auditor, the IRB, or other regulatory authorities, such as the Office of Human Research Protections, or the FDA, for study audits or reviews. It also provides the research team an easy reference to study information.

ESSENTIAL DOCUMENTS THAT SHOULD BE STORED IN A REGULATORY BINDER

The essential documents that should be maintained within the Regulatory Binder are documents that demonstrate compliance with the standards of GCP and all applicable regulatory requirements. Although not regulation, the FDA adopted the International Conference on Harmonization (ICH) Guidelines (ICH GCP E6 Section 8) as guidance to the maintenance of trial documents. ICH GCP E6 4.9.4 indicates that an 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. It also states that an investigator/institution should take measures to prevent accidental or premature destruction of trial documents. ICH GCP E6 Section 8 specifies which documents are considered essential and provides an explanation of the purpose of the documents.

MAINTENANCE OF THE REGULATORY BINDER

Maintenance of the Regulatory Binder is often delegated to other members of the research team. However, the Principle Investigator is ultimately responsible for the maintenance and accuracy of the regulatory binder/files. The organization and contents of the binder should be easy to understand by someone who is not familiar with the study. Patient confidentiality should be maintained by blacking out patient names and using subject numbers in reports (e.g. adverse event reports). Binders should be maintained in a secure location, preferably a locked cabinet, and at a minimum a locked office.

ORGANIZATION OF THE REGULATORY BINDER

The Regulatory Binder needs to be organized in such a manner that allows specific documents to be found easily. The key to filing is "consistency". Documents should be filed in reverse chronological order (newest versions on in the front). Various formats are acceptable. However, the contents should be consistent and contain the following:

REGULATORY BINDER TABS AND CONTENTS

- Protocol and Amendments
    - The initial protocol and ALL amendments with documented IRB and sponsor approvals
- Informed Consent & Assent
    - ALL approved versions including other languages
    - Each version in a foreign language should also have a Certificate of Translation
- Continuing Reviews
    - This section should contain all approval letters from the IRB
    - The Study completion/termination report should also be placed in this section upon completion of the study
- 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
    - For each investigator
    - Demonstrates qualifications of ALL investigators
    - Copies should be up to date
    - Copies should be signed and dated.
- Serious Adverse Events
    - Copies of each report should be maintained here
    - Documentation of receipt from the IRB, sponsor, FDA, and OBA as applicable for each report
- IND Safety Reports
    - Copies of each report should be maintained here
    - Documentation of receipt from the IRB for each report
- Additional IRB Correspondences
    - Regarding approval process of protocol, amendments
        - Submissions, stipulations, responses to stipulations
        - Does not need to be entire submission packet
        - 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
- 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
- Investigator's Brochure (IB)
    - ALL versions of the IB and updates
    - Contains scientific information for the investigational product(s)
    - For FDA approved agents, file a copy of the package insert
- Recruitment & Advertisement Materials
    - Copy of all recruitment and advertisement materials with documented IRB and sponsor approvals
- Sponsor Correspondences
    - Pre-study correspondences as appropriate
    - Details processes and procedures for study conduct
    - Phone Logs
    - Site visit letters/summaries
- Other Correspondences
    - Any miscellaneous protocol-related correspondences
- 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 the protocol
    - If using results for a specific patient as the reference ranges, blacken out all patient specific identifiers, copy and then place in binder
- 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 the study
- Site Visit Log
    - Log in which monitors will document their visits
    - Site staff need to have a place to initial/verify that a monitor was present on the specific dates documented
    - For consecutive days, each day should be entered separately
- Training Records/Certificates/Inservices

    - The principle investigator should ensure that there is adequate training for all staff participating in the conduct of the study and document such training such as:
        - Copy of human research training certificates for all study staff
        - Additional training certifications (e.g. chemo certification, phlebotomy, etc.)
        - Copies of sign-in sheets or signed attendance lists conducted on a specific study
- Delegation of Authority Log/Signature List
    - List of individuals (including signature and initials) for all persons that are delegated study related activities by the principle investigator
    - This log should be updated in a timely manner as new personnel are added and/or study roles change.
- Pharmaceutical Information
    - Drug Accountability documentation including shipping and dispensing records
    - Samples of labels attached to investigational product containers
    - Decoding procedures (if not detailed in the protocol)
    - This documentation may be kept in the pharmacy binder and a copy in the Regulatory Binder.
- Blank set of Case Report Forms
- Record of Retained Tissue or Fluid Samples
- Notes to File
    - When something unusual happens in a clinical study, it is common to document the incident with a not to file in the regulatory binder or other study files.
    - Incidents that are often documented include:
        - Decisions made
        - Instructions from the study sponsor
        - Problems experienced
        - Other matters that are important to remember in order to understand what happened during the study
    - If you think there is a chance that a data query, site monitor, auditor, or inspector will ask a question and find the note useful in understanding what happened in the study, then it is worth documenting in a note to file.
    - A good note to file includes:
        - Date, author, and subject of the note
        - What happened
            - Who, what, why, when, where, and how
        - Why is the incident important
        - What was done to address the incident
        - What will be done to prevent or mitigate similar incidents in the future.

REFERENCES

https://ccrod.cancer.gov › confluence › download › attachments › Regulatory Binder

https://nccih.nih.gov › Regulatory_Binder_Checklist_ver3_07-17-2015

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

https://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial/