Guidelines for Setting Up a Regulatory Binder

Prepare for an audit

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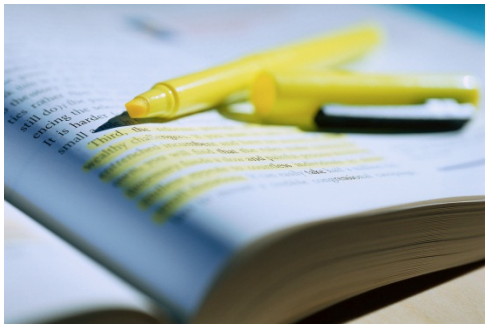
Introduction

- A study should be organized and well planned BEFORE the initiation of patient accrual.
- Investigators may use any system that enables them to present study documents in a well-organized, up-to-date, complete, convenient way that is easily accessible to monitors and auditors.
- If documents are organized and maintained in such a systematic way, the PI should easily be in compliance with regulations and should do well on any audit.

Introduction

- A regulatory binder or file contains all study-specific information and regulatory documentation.
- The regulatory binder is part of the GCP Guidelines (GCP E6 Section 8).
  - It is recommended that ALL intervention trials have one regardless of sponsorship. For sponsored trials, the sponsor also maintains a mirror image of the site's regulatory binder.

Course Objectives



- Describe the purpose of the Regulatory Binder
- List the essential documents found in a regulatory binder
- Describe the purpose of the screening, enrollment and site visit logs.
- Describe when it may be appropriate to centralize essential documents.

What is a Regulatory Binder?

- Contains all study – specific information and regulatory documentation. It is not used for data collection.
- Terms used to describe a Regulatory Binder:
  - Regulatory Files
  - Study Binder
  - Administrative Binder
  - Investigator's Study Files
  - Investigator Binder

Purpose of a Regulatory Binder

- It organizes essential documents
- Provides easy access to essential documents by the trial monitor, auditor, IRB or regulatory authorities (OHRP, FDA) for auditing purposes
- Allows research team members to reference information

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 ICH Guidelines (ICH GCP E6 Section) have been adopted by the FDA as a guidance, not regulations.

Guidance Documents

- ICH GCP 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 8
  - Specifies which documents are considered essential
  - Gives explanation of purpose of documents: http://www.fda.gov/cder/guidance/959fnl.pdf

Maintenance of the Regulatory Binder

- PI 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

- Rule for filing is Consistency
- Needs to be organized in a manner that allows specific documents to be found easily
- Various formats are acceptable
  - Some sponsors have required format

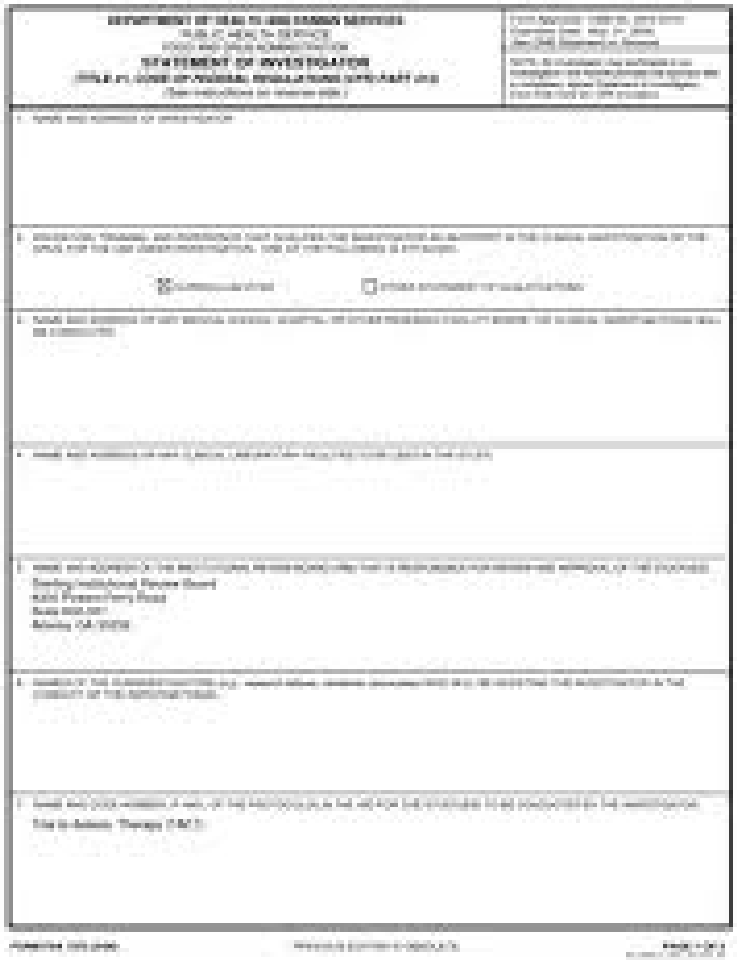
Regulatory Binder Contents….

- Protocol and Amendments
  - Initial protocol, revised versions and all amendments
  - Investigator's Signature pages
- Informed Consent
  - All IRB approved versions

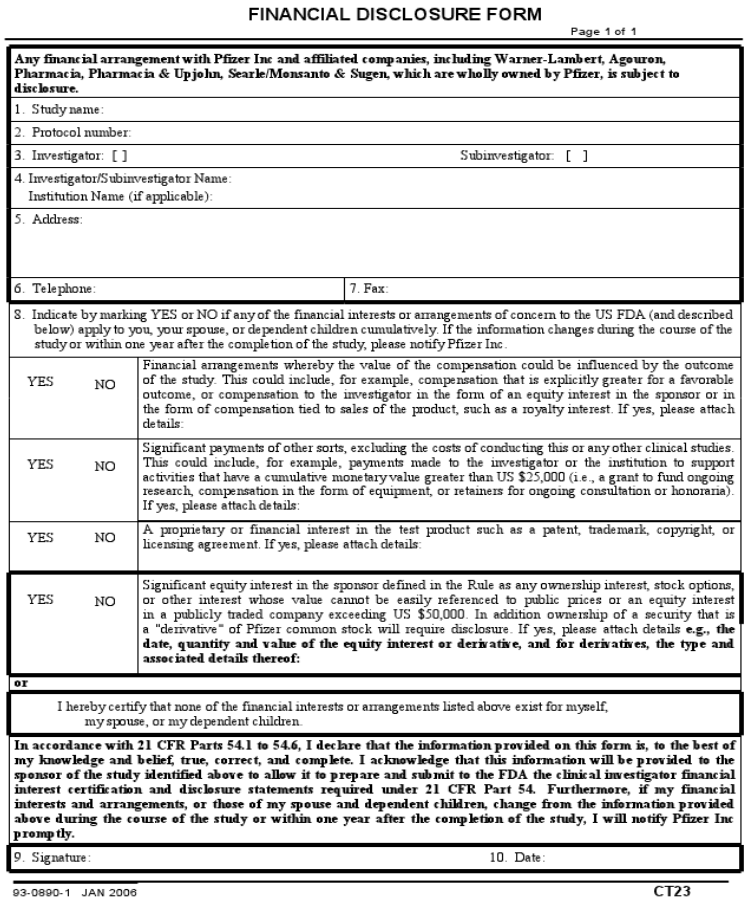
Regulatory Binder Contents….

- Curriculum Vitae
  - Demonstrate qualifications of all investigators and associate investigators
  - Copies should be signed and dated. Updates are required every two years, or specified by Sponsor
- FDA 1572 Form for all IND Trials
  - Copies of All versions signed and dated
  - Investigator's Agreement
- Device approval & Indications
  - Significant vs. non significant risk device determination
- Financial Disclosure Form
  - Provided by Sponsor

FDA 1572 Form



Financial Disclosure Form



FINANCIAL DISCLOSURE FORM

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Any financial arrangement with Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto & Sugen, which are wholly owned by Pfizer, is subject to disclosure.

1. Study name:

2. Protocol number:

3. Investigator: [ ] Subinvestigator: [ ]

4. Investigator/Subinvestigator Name:
Institution Name (if applicable):

5. Address:

6. Telephone: 7. Fax:

8. Indicate by marking YES or NO if any of the financial interests or arrangements of concern to the US FDA (and described below) apply to you, your spouse, or dependent children cumulatively. If the information changes during the course of the study or within one year after the completion of the study, please notify Pfizer Inc.

YES	NO	Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. If yes, please attach details:
YES	NO	Significant payments of other sorts, excluding the costs of conducting this or any other clinical studies. This could include, for example, payments made to the investigator or the institution to support activities that have a cumulative monetary value greater than US $25,000 (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If yes, please attach details:
YES	NO	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement. If yes, please attach details:
YES	NO	Significant equity interest in the sponsor defined in the Rule as any ownership interest, stock options, or other interest whose value cannot be easily referenced to public prices or an equity interest in a publicly traded company exceeding US $50,000. In addition ownership of a security that is a "derivative" of Pfizer common stock will require disclosure. If yes, please attach details **e.g., the date, quantity and value of the equity interest or derivative, and for derivatives, the type and associated details thereof:**

or

I hereby certify that none of the financial interests or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.6, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. I acknowledge that this information will be provided to the sponsor of the study identified above to allow it to prepare and submit to the FDA the clinical investigator financial interest certification and disclosure statements required under 21 CFR Part 54. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the completion of the study, I will notify Pfizer Inc promptly.

9. Signature: 10. Date:

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Regulatory Binder Contents….

- Adverse Event Reports
  - Copies of Reports
  - Documentation of receipt from IRB, Sponsor, FDA, as applicable
- IND Safety Reports
  - Copies of reports
  - Documentation of receipt from IRB (Annual Summary)

Regulatory Binder Contents….

- IRB Correspondence
  - Regarding approval process of protocol, amendments and cont. reviews
    - Submissions, recommendations, responses
    - Trail of the process
    - Approval Letters
    - Any documentation clarifying an issue regarding conduct of the study (expired studies)

Regulatory Binder Contents….

- IRB Membership Lists
  - Copy of ALL IRB members and any changes throughout the study.
  - UPR-MSC provides a letter stating the reasons for not providing this Membership List
  - FWA Documentation
  - If cooperative agreement in place, documentation that selected IRB of record accepts the other institution
- Subject Identification Code List
  - Confidential list of the names of all patients with their study Group assigned and ID number
  - Maintained only at the site
  - Allows the PI or Institution to quickly identify study patients in case of an emergency

Regulatory Binder Contents….

- Investigator's Brochure (IB)- scientific information for the investigational product
  - All versions and updates
  - For FDA approved drugs, file a copy of the Package Insert
- Recruitment and Advertisement- (brochures, flyers, etc.)
  - Document IRB and Sponsor Approvals

Regulatory Binder Contents….

- Sponsor Correspondence
  - Pre-study correspondence
  - Details processes and procedures for study conduct
  - Phone logs/e-mails
  - Site visit letters
- Other Correspondence
  - Any miscellaneous protocol-related correspondence.

Regulatory Binder Contents….

- Laboratory Certification
  - CLIA certifications
  - Laboratory Certifications
- Laboratory Normal Ranges
  - Copy of normal ranges for all labs/tests included in protocol with the Effective date
  - Usually are provided by the Reference Lab

Regulatory Binder Contents….

- Subject Screening Log
  - Patients who entered pre-trial screening period
  - Document why potential subjects were not included in study
- Subject Enrollment Log
  - Chronological enrollment
- Site Visit Log
  - Documentation of Monitor's visit
  - For consecutive days, each day is entered separately
- Deviation Log – (Provided by Sponsor)

Regulatory Binder Contents….

- Blank set of Case Report Form (CRF)
  - Provided by the Sponsor
- Delegation of Authority Log/Signature List (Staff Signature Log)
  - To delegate certain study-related tasks to others
  - Must be updated in a timely manner as new personnel are added and/or study roles change

Protocol version

Staff Signature Log

Study Title: IRB #

Name	Role	Signature	Initials	Date Trained	Authorization (See List below)	Dates of Involvement
						From: To:
						From: To:
						From: To:
						From: To:
						From: To:
						From: To:
						From: To:
						From: To:

* The above personnel have been authorized to perform the following study functions:

1.	Collect study data	6.	Drug Return Procedures	11.	Sign CRFs
2.	Communicate with Sponsor	7.	IRC approved to obtain informed consent	12.	Subject selection/screening
3.	CRF entries/corrections	8.	Obtain study measurements	13	Other: _____
4.	Dispense study medications	9.	Perform physical exams/study procedures	14.	Other: _____
5.	Drug Accountability	10.	Review medical records/access PHI	15.	Other: _____

By signing this form, I, the Principal Investigator for this study, agree to take responsibility of the day-to-day conduct of the study, to delegate only when appropriate, and to delegate to qualified individuals who have met institutional research education requirements and have been adequately trained in the protocol and their study-related duties and functions before any involvement in the study. I confirm that it is my responsibility to ensure that any new staff added during the course of the study will also sign this form and be adequately trained before they become involved in any study-related duties.

By signing this agreement, I agree to conduct this study according to FDA and/or HHS regulations, and HSPO policies and procedures. I further agree to internal and external auditing of this study.

_____ _____

Signature of Principal Investigator Date

Regulatory Binder Contents….

- Training Records/Certificates/Inservices
  - Adequate training for all staff
  - Copies of Professional Licenses (RN, MD)
  - Keep evidence of training such as:
    - Human Research Training for all study staff
    - HIPAA Training for all study staff
    - Additional training certification of study staff (phlebotomy, vital signs, IATA, Drug accountability, etc.)
    - Sing-in copies of inservices conducted on a specific study

Note: Not listed in ICH GCP guidelines but FDA may ask to see these documents

Regulatory Binder Contents….

- Pharmaceutical Information
  - Drug Accountability
    - Shipping and Dispensing Records
    - Sample of labels attached to investigational product containers
    - Documents typically in the Pharmacy Binder but when the study is completed, a copy is placed in the Regulatory Binder

- 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.
- Incidents can include:
  - Decisions made
  - Instructions from the sponsor
  - Problems experienced
  - Other matters that are important to remember if one is to understand what happened during the study

Notes to file

- A good note to file includes:
  - Date, author, subject
  - What happened? (who, what, when, how, why)
  - Why is the incident important?
  - What has been done to address this incident?
  - What will be done to prevent similar incidents?

General Rules for Maintaining Regulatory Binder

- Binder contents/organization need to be easily understood by someone who is not familiar with the study
- Black out patient names and use subject numbers in reports (AE reports, lab reports)
- Patient confidentiality needs to be maintained
- Keep binders in a secure location
- File documents in reverse chronological order
- Do not use binders to hold irrelevant papers (post-it, notes to yourself)

Centralization of Files

- If multiple studies have the same regulatory documents, it is acceptable to file in one binder
- Place note to file in each study's regulatory binder indicating the location of centralized files
- Examples:
  - Laboratory certifications and normal ranges
  - IRB membership lists
  - CVs and staff certifications

Helpful Hints

- Flexibility - What works for your study?
- Ask colleagues for advice/tips
- Attention to detail
  - Be careful to file documents into the correct study binder
- Keep it updated
  - 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
- Keep in mind the purpose of the binder: to document in compliance with GCP and regulatory requirements

Questions

- For general information and assistance:

Human Research Subjects Protection Office
UPR Medical Sciences Campus
Second Floor Suite A-236 Main Building
Phones: (787) 758-2525 Exts. 2510-2515
opphi.irb@upr.edu

References

- International Conference on Harmonization Good Clinical Practice Guidelines (ICH-GCP)-E6 Efficacy http://www.ich.org
- Ginsberg, D. The Investigator's Guide to Clinical Research. 3rd edition. Boston, Thompson, Centerwatch, 2008
- Woodin, K.E., Schneider, J.C. The CRA's Guide to Monitoring Clinical Research. Boston, Thompson, Centerwatch, 2003