Maintaining Essential Regulatory Documents

Presented by:
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References for Essential Regulatory Documents

- International Conference on Harmonization (ICH) Good Clinical Practices (GCP)

- 45 Code of Federal Regulations, Part 46 – Protection of Human Subjects

- DMID Regulatory File Document Guidelines - http://www.niaid.nih.gov/labsandresources/resources/dmidclinrsrch/documents/regulatoryfiledocumentguidelines.pdf

- Regulations of In-Country Health Regulatory Authorities (HRAs)

ICH GCP Guidelines

- Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a research study and the quality of the data produced.

- 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.

- Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a clinical study by the investigator, sponsor and monitor.

Reference: ICH GCP 8.1

Objectives

At the end of this overview, you will be able to:

- Know what essential documents you must file:
  - Before the clinical phase of the study begins
  - During the clinical conduct of the study
  - After completion or termination of the study

- Develop a plan for maintaining and submitting your site's essential documents

Essential Regulatory Documents

Establish

The Site Essential Documents Binder

Review

Essential Document Review Worksheets

Submit

Submission and Notification

CEIRS Essential Regulatory Documents

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Review

Submit

The Site Essential Documents Binder

- Standard Binder Tabs
- Reference Documents and Tools
- Customizable Templates
- Annotated Sample Documents

d Binder Tabs

A **Note to File** in the corresponding binder section must identify where electronically stored files are located.

ESSENTIAL DOCUMENT BI	ESSENTIAL DOCUMENTS TO BE FILED	Before	During	Completion/ Early Close-out	Listed in Document Review Worksheet
IRB/IEC Approval Letters	CRF(s) (if applicable)				**X**
	ICFs and translations				
	Participant's any written informati				
	Participant's recruitment advertisement (if used)				
	Participant compensation (if any)				

The **IRB/IEC Approval Letters** and **IRB/IEC correspondence** must be translated into English.

The **Essential Document Review Worksheets** list the required essential documents by phase of the clinical study.

Informed Consent Forms (ICF) must be written in a language familiar to study participants.

Reference Documents and Tools

University
School of Medicine
Department of Epidemiology
123 4th Avenue
City, State

Note to Study File

Date: 15/Jan/2008

To: DMID Protocol # XX-XXXX Study File

From: John Jones, MD
Principal Investigator
University

J. Jones, MD

Re: DMID Protocol # XX-XXXX
University

Issue: Consenting subjects with obsolete Informed Consent Form.

On 10/Jan/2008, I noted that 15 subjects had been consented using version 1 of the Informed Consent (12/Oct/2007) although we had received IRB approval of version 2 (20/Oct/2007) on 31/Oct/2007. All subjects were screened and entered the protocol in Dec/2007. This is a two visit protocol and their participation had been completed as of 08/Jan/2008.

Resolution: This issue was reported to the IRB (11/Jan/2008) who stated that re-consenting would not be required in this case.
The IRB did require that we review our procedures and present Human Participant Protections training to all staff.

Comments:

- Site personnel have been re-trained in Human Participant Protections
- Site SOP was resolved to include discarding old forms when new consents are approved by the IRB
- Study Coordinator will verify all obsolete Informed Consent Forms have been discarded upon approval of a new version.
- Site QA/QM manual was modified to add procedures regarding regularly scheduled checks on future consenting of subjects.

Effective date of resolution: 15/Jan/2008

Version to be updated

SAMPLE

Notes to File Guidelines

- Printed on institutional letterhead
- Formatted as follows:
  - Date (MM/DD/YYYY):
  - To:
  - From:
  - Re:
- Defines the issue and describes the resolution or pending corrections
- Documents the preventive actions taken to avoid recurrence
- Includes the effective date of resolution

Customizable Templates

DMID Protocol No:
Protocol Title:
Site Name and Number:
PI's name:

STUDY PERSONNEL SIGNATURE/RESPONSIBILITY LIST

PRINTED NAME	TITLE	SIGNATURE	STUDY TASKS	INITIALS	START DATE/ END DATE	ID CODE if applicable	PHONE # and E-MAIL ADDRESS
	Principal Investigator						
	Sub-inv						
	St Coordina						

List individuals' delegated study relate
Signature/initials required for all perso
and/or corrections to Case Report For
In addition, you may need to list other
Update as personnel, roles and/or study
Copy of completed form to be collected by Monitor at st

ms
applicable if an eCRF)

...ed Study Product Dose Administration 16. Other_____
8. Study Product Accountability

Principal Investigator Signature (Close Out):_____ Date:_____

DMID-CROMS for CEIRS Regulatory File Guidelines
Version to be updated

Page____ of ____

The **signatures and initials** to make entries and/or co Forms (CRF) must

This log lists the **names and titles of all study personnel**, their **delegated study tasks**, and the **start/end dates** for these responsibilities.

The **Principal Investigator must sign and date** the completed form as part of the clinical study close out.

Annotated Sample Documents

University of Connecticut Health Center Institutional Review Board
1000 Grand Avenue
Farmington, CT 10122
(777) 638-0000

Notification of IRB Approval
Protocol #: 03-340; UCHC
Date: 09/30/2008

To: Angela Smith, MD
Internal Medicine
GH-407
From: Peter Fox
IRB Chair
1000 Grand Ave.

Title of Protocol: A Phase II, Randomized, Double-Blind, Placebo-controlled clinical study of H5N1 influenza vaccines in H5 naive adults. Sponsor Protocol # 12-342
Version Number: Version 2.0, 20-Jan-2008
Sponsor: NIH-NIAID
IRB Review Type: Full Board
IRB Approval Date: 9/25/2008
IRB Expiration Date: 9/24/2009

The above project has been reviewed and approved by the UCHC IRB, Assurance # FWA0000000XXXX. During the review, the IRB specifically considered (a) the risks and anticipated benefits, if any, to the participants; (b) the selection of participants; (c) the procedures for securing and documenting informed consent; (d) the safety of participants; and (f) the privacy of participants and confidentiality of the data.

As the Principal Investigator, you are responsible for submitting in writing, any changes in study procedures to the IRB for review and approval prior to implementation unless the change is necessary for the safety of participants. Investigators must also be aware of the definition and criteria for reporting Unanticipated Problems as described in the "OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others ……", if applicable. When discovered, Unanticipated Problems must be reported to the appropriate authorities and documented in the regulatory file [http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm].

The IRB can and will terminate projects that are not in compliance with the requirements set forth above.

Additional documents were approved by the IRB. If a new informed consent form or recruitment material were approved at this time, please discontinue use of any prior approved informed consent forms or recruitment document(s). Only the most recently approved version of the informed consent forms and recruitment materials bearing the UCHC IRB watermark may be used. Please refer to the *WolfIRB - New Documents Report* for the listing of approved documents.

Sincerely,
Peter Fox, MD, PhD
Institutional Review Board Chair

Version will be provided by the site's IRB/IEC
CEIRS_Approval IRB Letter Sample

SAMPLE

IRB Approval Letter

- Uses IRB letterhead with identifiers and address
- Lists the full protocol title
- Includes the version number and version date of the approved protocol
- Provides date of approval and/or duration of approval
- Lists additional documents approved and specifies version numbers and version dates

Annotated Sample Documents

WolfIRB
PI: Angela Smith
IRB # 03-340, UCHC

New Documents Report

HISTORY

Attachment Name	Category	Ver	Attached
Sponsor Protocol_v2.0_20Jun2008	Grant/Protocol	.2	08/25/2008
Informed Consent Form_v2.0_18Aug2008	Consent/Assent	.4	08/25/2008
PregnancyConsent_v4.0_23Aug2008	Consent/Assent	.1	08/25/2008
BirdFluAd1_v1.0_13Jul2008	Recruit Matl	.1	08/25/2008
PSA_v1.0_16Jul2008	Recruit Script	.1	08/25/2008
BirdFluFlyer_v2.0_08Jul2008	Recruit Poster	.2	08/25/2008
Recruit_letter_v1.0_19Jul2008	Recruit Mail	.2	08/25/2008
InvestBroch_v10	Investigator B	.1	08/25/2008
Package_insert_BLA	Investigator B	.1	08/25/2008
Phone screen_v8.0	Misc	.2	08/25/2008
Participant Info_v3.0_15May2008	Misc	.1	08/25/2008
Screen_enroll_log_v4.1_10Feb2004	Misc.	.1	08/25/2008
Informed Consent Form _v1.0_16Jul2008	Consent/Assent	.3	7/23/2008
HIPAA authorization_v1.1	Consent/Assent	.1	7/23/2008
Study Schedule v0.7	Misc.	.1	7/23/2008
SponsorProtocol_v1.0_14Apr2008	Grant/Protocol	.1	7/23/2008
Figure1_Descrptionn of Study_v1	Misc.	.1	7/23/2008
BirdFluFlyer_v1.0_06May2008	Recruit Poster	.2	7/23/2008

mm/dd/yyyy

SAMPLE

View Attachments Page

- Lists documents the IRB/IEC has reviewed and approved
- Shows an example of a History Log received from an eIRB submission
- Standardizes the attachment names
  - File Name
  - Version Number
  - Version Date
- Matches document header/footer
  - Version Number
  - Version Date

Best Practice Recommendations

- If you elect to use only electronic copies of particular documents, observe the following guidelines:
  - Place a paper placeholder that lists the electronic location in the relevant location of the binder,
    Or
    Place a paper placeholder in one location in the binder listing all documents stored only in electronic format with the specific electronic path for each item.
  - Limit electronic-only documents to those easily accessible by site staff,
    And
    Provide easy access to relevant electronic materials by an inspector, auditor, or clinical monitor during a site visit.
  - Maintain a controlled electronic location that is regularly backed up and not in danger of disappearing or changing in the foreseeable future.

Questions

CEIRS Essential Regulatory Documents

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Essential Document Review Worksheets

- **Before** the Clinical Phase of the Study Begins
- **During** the Clinical Conduct of the Study
- **After Completion or Termination** of the Study

Reference: CEIRS Clinical Research Support

Essential Document Review Worksheets

Before the Study Begins:

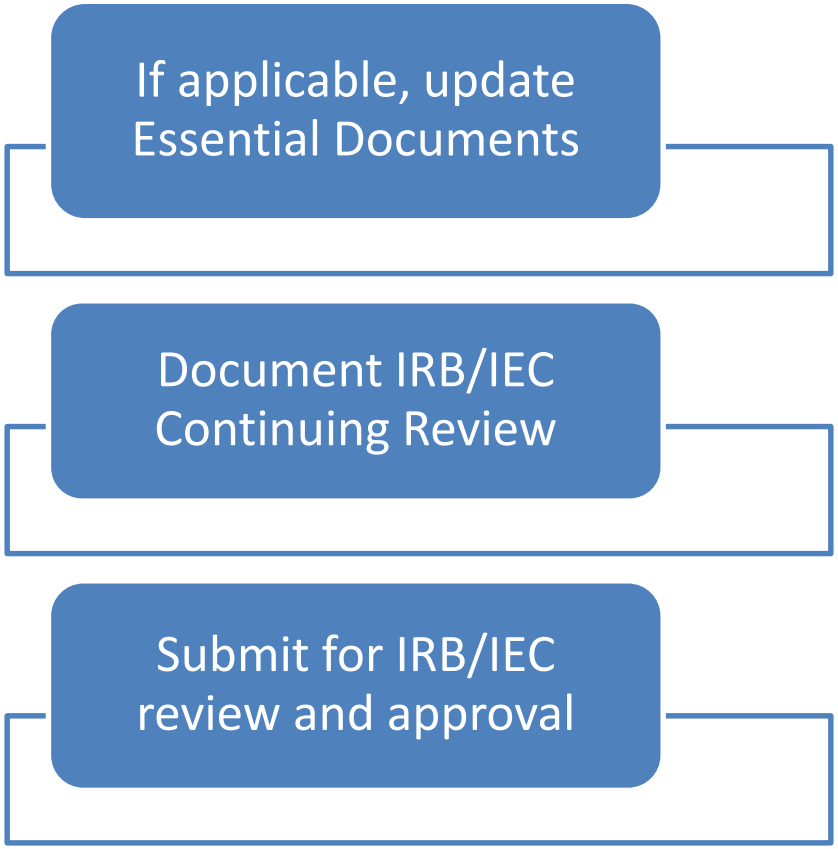
1. Investigator Curriculum Vitae
2. IRB/IEC Review and Approval Documentation
3. IRB/IEC-Approved Informed Consent Form & Additional Approved Documents
3. Laboratory Credentials Certification Equivalent to CLIA
5. Laboratory Reference Ranges
6. OHRP Federal Wide Assurance
7. Principle Investigator Licensure
8. Protocol Signature Page

Essential Document Review Worksheets

Verified	Essential Documents – Before Study	Standard Binder Tab
Yes	1. Investigator(s) CV(s)	Investigators and Sub-Investigators - Qualifications
Yes	2. IRB/IEC Review and Approval Documentation	IRB/IEC Approval Letters
Yes	3. IRB/IEC-Approved Informed Consent and Additional Approved Documents	Information Given to Participants
Yes	4. Laboratory Credentials/Certification equivalent to CLIA	Laboratory Credentials/Certification
Yes	5. Laboratory Reference Ranges	Normal Value(s)-Ranges
Yes	6. OHRP Federal Wide Assurance	IRB/IEC
Yes	7. Principal Investigator Medical Licensure	Investigators and Sub-Investigators - Qualifications
Yes	8. Protocol Signature Page	Signed Protocol Amendments

Essential Document Review Worksheets

During the Conduct of the Study



- If applicable, update the following
  - Curriculum Vitae (CV)
  - Principal Investigator Licensure
  - Laboratory Reference Ranges
- Document IRB/IEC Continuing Review
- Submit to IRB/IEC for approval
  - Changes in Study Site Status
  - Protocol Amendments
  - Revisions to Informed Consent Form

Essential Document Review Worksheets

After Completion or Termination

- List full Protocol title and DMID Protocol number
- Use IRB letterhead with app address
- Specify study documents re
- Date approval documentati
  - Dates of approval
  - Duration of approval
- Have IRB chairperson or aut representative initial or sign

IRB/IEC Closeout Documentation

IRB/IEC Termination Documentation

Final Study Report Approval

Questions

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Submission and Notification

- IEC/IRB and In-Country Health Regulatory Authority (HRA)
- Pre-Study Process
- During and After Study Processes

Site Binder Maintenance

Maintain the Essential Document Binder or regulatory documents in a separate, secure location for each project

- Maintain all document versions:
  - Protocols
  - Informed Consent Forms
  - Case Report Forms (CRF)
- File documents within each section in reverse chronological order by appropriate clinical phase
- Maintain all IRB/IEC submissions, acknowledgements, approvals, and other communication in the same section
- Maintain CVs, relevant licensure, and applicable training records
- Maintain correspondence with study personnel
- Maintain significant correspondence related to the conduct of the study

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Questions?