Documentation

WINTER - ACADEMY FOR RESEARCH PROFESSIONALS

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Presented by:
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Clinical Trials Specialist
Objectives:

- Background
- Understanding Essential Documents
- Regulatory Binder Management
- Documentation & Record Keeping
- Electronic Documentation
- Resources

Disclaimer Disclosure: No conflict of interest
Background

Elements of a “Quality” Clinical Study

- Scientifically valid and ethically sound experimental design
- Qualified and trained personnel
- Adequate monitoring
- Document management
- Current, complete, and accurate data collection
- Adequate protection of subjects – rights, safety, and well-being
Research conduct is required to comply with laws, regulations and guidelines by agency, local, state, federal and international guidance. Conduct may be required to follow GCP Guidelines depending on the trial, sponsor, location, and/or the government in which data from the trial is going to be submitted. High standards may occur with overlap in the standards expressed in each. At the same time, each may also cover certain unique standards.
Background

Regulatory Oversight

Code of Federal Regulations (CFR)
21 CFR: 11, 50, 54, 56, 312, 314 and 45 CFR 46

International Council of Harmonization (ICH) Guidelines
E6 GCP

Provide Standards and Guidance in Conduct of Clinical Research

- Rights, safety, and well-being of subjects
- Roles and Responsibilities of Investigators and Research Staff
- Study conduct and protocol management
- Safety reporting
- Documentation and Record Keeping
Essential Documents

- **Documents** that “individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced”

- “Serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and the applicable regulatory requirements”

- Minimum list of **Essential Documents** can be found in ICH GCP E6(R2) Section 8.

**TIP: Documentation should “stand on its own” in telling the “story” of the study. The PI is responsible for all protocol activities including the maintenance and storage of the study documentation, but must rely on the research coordinator and research team to comply with the guidance.**

Section 8 ICH E6 GCP
Examples:

- Original paper clinical visit note by a clinical licensed professional
- Electronic Medical Record (EMR) notes or reports scanned into the EMR from outside medical offices
- Test results printed from an institutional EMR
- Pathology reports and/or procedure(s) results
- Specific forms created by Clinical Research Unit to record mandatory process required by the protocol (i.e. PK sample statement log, patient drug diary, procedure orders)
- Any original source documentation or handwritten notes

**TIP:** All Source Documents - original or electronic - must have a signature and date, by the person creating the source. When applicable signed by the Principal Investigator (PI).
Regulatory Binder

Binder has many different names:

- Investigator Binder
- Regulatory Binder
- Study Binder
- Investigational Site File (ISF)
- Trial Master File (TMF)
Regulatory Binder

Purpose

• **ORGANIZE** filing of study *Essential Documents*
• **MANAGE** all aspects of the trial conducted at the site
• **EVALUATE** trial conduct and quality of data produced
• **DOCUMENT COMPLIANCE** by the investigator and sponsor to the standards / requirements of: FDA, IRB, NIH, Good Clinical Practice (GCP) and ICH
• **DOCUMENT** qualifications, credentials, and training

Section 8.1, 8.2, 8.3, 8.4 ICH GCP E6
Regulatory Binder

Essential Documents Timeline:

1. **BEFORE** the study starts
2. **DURING** the conduct of the study
3. **AFTER** completion or termination

**TIP: Keep the binder current and up-to-date at all times**
Regulatory Binder

Inspection and Monitoring Expectations

- **Data Integrity** - efficacy and safety data
- Evidence of subject **Rights, Safety, and Welfare** are protected
- **Compliant** conduct with applicable regulations and requirements
- **Availability** - for inspection and copying (e.g. FDA, Sponsor, CRO)
- **Retain** - for appropriate length of time
- **Preserve** - independently at clinical site and meets regulatory requirements
Who can conduct an inspection/or monitor your research study?

1. Institutional Review Board (IRB)
2. Joint Office for Research Billing (JOC)
3. Sponsor/Clinical Research Organization (CRO)
4. Department of Health and Human Services (OHRP)
5. Food and Drug Administration (FDA)
6. Cooperative Group/NIH
7. Grant Accounting/Billing
8. VA Research Compliance Officer (RCO)
9. All of the above
10. Only 1, 3, and 5

ANSWER: #9
Regulatory Binder

- **Investigator** maintains at clinical site
- Store binder in a **safe, secure location** ONLY accessible to research study team
- Subject-specific documentation and information (e.g., signed consent forms, test results, and completed case report forms, should be maintained separately in a subject binder/file.
- Document locations of other information, if located separate from regulatory binder (note-to-file or log)
- **NEVER** discard old versions of documents!
Regulatory Binder

Best Practice Recommendations

- Organize and order the sections to facilitate easy use and reference
- Store study documents in Reverse Chronological Order
- Place newest items within a section at the front

Multi-site Studies: The Lead Site may choose to customize a Checklist for the study and provide to all participating sites.
# Regulatory Binder Checklist of Essential Documents

## TABLE OF CONTENTS

- Protocol & Amendments
- Protocol Training Logs
- Informed Consent Documents/Patient Information
- IRB Documentation Approvals/Correspondence
- Curriculum Vitae (CVs)
- Investigator Qualification Documentation
- Clinical Investigator Brochure (IB)
- FDA Documents
- Financial Disclosure Forms (FDF)
- Study Communications/Correspondence Site-Sponsor-Governing
- Delegation of Authority Log/Roles and Responsibilities / Signatures
- Clinical Research Training/Certifications
- Screening/Enrollment Logs
- Signed Consent Documents
- Investigational Product/Device Accountability Logs
- Specimen Tracking Log
- Serious Adverse Event (SAE)/Safety Reports/Unanticipated Event
- Data Safety Monitoring Documents
- Study Protocol Deviation Forms
- Clinical Site Monitoring Visits
- Notes-To-File (NTFs)
- Case Report Forms (blank master copies)
- Subject Logs
Protocol & Amendments

- IRB-approved protocol
- IRB-approved protocol amendments
- Signed principal investigator (PI) signature pages for all protocol versions
- Log of protocol changes
IRB Documentation

- IRB Federal Wide Assurance Number
- Updated IRB Roster (optional)
- IRB Registration (optional)

Link to OHRP Database - FWA & IRB Registration:

According to the Department of Health and Human Services, the Federal Policy for the Protection of Human Subjects (also known as the Common Rule), which requires institutions to ensure that the risks to subjects are minimized and that the potential benefits to subjects justify any potential risks to subjects, the Department of Health and Human Services has issued a final rule to simplify the current regulations that govern human subject research. The final rule was published in the Federal Register on January 19, 2018. The rule is expected to improve the way research is conducted and to make it easier for researchers to obtain approval for their studies. The rule simplifies the requirements for obtaining IRB approval, and it also provides clearer guidance on how to conduct research in a way that is consistent with the principles of respect for persons, beneficence, and justice. The rule also includes provisions for the protection of vulnerable populations, such as children, pregnant women, and prisoners. The rule is expected to take effect on January 19, 2018, and it will apply to all research conducted in the United States.
IRB Approvals & Correspondence

- Original IRB New Project application / submission
- IRB approval letters
- IRB Annual Continuing Reviews
- Project closure notification
- IRB-approved advertisements, brochures
- IRB-approved Participant Information Sheets
- IRB-approved blank Case Report Forms (CRFs)
Informed Consent Documents

- IRB-approved/stamped *(clean copy)*:
  - Consent documents
  - Consent summaries
  - Assent documents
  - Short form consents for non-English speakers/readers

**Note: Keeping a log of Informed Consent Form versions can be helpful**

- Retain all original, **signed** consent documents:
  - Current IRB approved/stamped version
  - Consent modification (e.g., protocol amendments requiring new version)
  - **Even if the subject withdraws consent or screen fails!**

- Store in one location - subject folder or separate binder
  - If stored separately, document the location in a Note-To-File
Investigator Qualification Documentation

- Up-to-date Curriculum Vitae (CV) for principal investigator (PI) and subinvestigator(s)
  - Include institution address, name, and date in header; with original signature and date in upper right hand corner
  - Institution address, name, and licensure need to mirror the information on the FDA 1572

- Current clinical professional licensure (dental, medical, nursing, pharmacy, etc.) for PI and co-investigators, if licensed

- Update CV and documents as the licensures expire or qualifications change
The Investigator’s Brochure (IB) is a document that summarizes previous findings and data, both clinical and nonclinical, on the investigational product(s) that are relevant to the study:

- Mechanism of action, potential risks
- Clinical pharmacology - peaks, AUCs, metabolites, drug interactions
- Safety information
- Toxicities – general, geno, carcino, and cardiac
- CMC - impurities, shelf life, substance uniformity
- Describes adverse reactions, the ‘expected’ adverse reactions associated with previous use of the investigational product
- Previous clinical trials and animal experiments

All Investigator’s Brochure (IB) amendments and versions need to be saved during the entire trial.
Who signs the Form FDA 1572?

1. Clinical Investigator (a.k.a. Principal Investigator)
2. Sponsor
3. Coordinator
4. FDA
5. Laboratory
6. All of the above
7. Only 1

**ANSWER: #7**

The investigator’s signature on this form constitutes the investigator’s affirmation that he or she is qualified to conduct the clinical investigation and constitutes the investigator’s written commitment to abide by FDA regulations in the conduct of the clinical investigations.
FDA Documents

- FDA Form 1571: Investigational New Drug Application (IND)
- FDA Form 1572: Statement of Investigator for IND studies (21 CFR Part 312)
- FDA Form 3674: Certificate of Compliance with requirements of ClinicalTrials.gov Data Bank
- FDA Financial Disclosure Form (21 CFR Part 54)
- Investigator Agreement for device studies (21 CFR Part 812)
- FDA approval or authorization letters
- FDA Correspondence Log (if applicable)

***Watch expiration dates on bottom of electronic forms!***

Go to FDA website for *most current versions* of FDA Forms to download:
[https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm](https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm)
Example Form FDA 1572: Statement of Investigator

**ALWAYS CHECK**
Expiration date

**FDA WEBSITE**
LATEST VERSION
1572 FORM

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<table>
<thead>
<tr>
<th>Form Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA 1572</td>
<td>Statement of Investigator</td>
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</tbody>
</table>

**FDA WEBSITE**
Example Form FDA 1571:

**FDA IND Application Number:** Must accompany any amendments, annual reports, IND safety reports or general correspondence the sponsor submits to the FDA about the IND.

Form Fields have changed!!

NEW

ALWAYS CHECK

FDA WEBSITE

for

LATEST VERSION

1571 FORM

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf
Financial Disclosure Forms (FDFs) certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or to disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR 54).

- Signed by the PI, sub-investigators, and each applicable research team member listed on the FDA 1572.
- Protocol title and number should match the title and number listed on FDA Form 1572.
- If any of the five financial interest questions are checked “Yes” a statement addressing the nature, amount of interest, arrangement or payment must be attached to the FDF.

Ancillary Disclosures:
- FDA Form 3410: Confidential Financial Disclosure Report
- FDA Form 3453: Certification: Financial Interests and Arrangements of the Investigators
- FDA Form 3455: Disclosure: Financial Interests and Arrangements of the Investigators

Delegation Records

The principal investigator (PI) is responsible to maintain a ‘List’ of appropriately qualified persons to whom significant trial-related tasks have been delegated (ICH section 4.1.5):

* Describe delegated study role tasks/supervision
* Identify training received/ongoing
* Identify dates of study involvement

Document evidence of three main points for delegating tasks:

1. Education
2. Experience (state licensures/curriculum vitae-CVs)
3. Training of individuals to whom task are delegated

Records may include:

- Delegation of Authority (DAF)
- Delegation of Responsibilities (DOR)
- Delegation of Authority Log (DOA)
Delegation Of Authority Log (DOA)
or Delegation Of Authority Form (DAF)

- The DOA is dictated by the ICH (under E6) and the FDA adapts as guidance.

- Log of Assigned Study Responsibilities and descriptions signed/dated by the Principal Investigator (PI)

- Documents PI delegation of trial related duties to other qualified and appropriately trained research study team members
  - The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

- **ALL** Research Team Members should be on the IRB application:
  - Start and Stop Dates of delegated duties
  - PRINTED name, initials, & original signatures
  - Descriptions of study responsibilities
Delegation Of Responsibility (DOR)

Staff specific form that documents Significant Trial Related Duties that an individual research team member is responsible for.

• Documents PI delegation of trial related duties to other qualified and appropriately trained research study team members
  ▪ The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

• Be sure to include ALL research team members on IRB application:
  ▪ START and STOP DATES of delegated duties
  ▪ PRINTED name, initials, & original signatures
  ▪ Descriptions of STUDY RESPONSIBILITIES
Delegation of Responsibilities Log (DOR)

Example:

**TIPS: The form is a generic example of the DOR form your sponsor/CRO may provide. You will be required to maintain for each study at your site. The form must be updated on an ongoing basis throughout trials to reflect any staff changes.**

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**Delegation of Responsibilities Log**

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Protocol</th>
<th>Site Number</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

List staff to whom the Principal Investigator (PI) has delegated significant study-related duties.

<table>
<thead>
<tr>
<th>Name</th>
<th>Responsibilities*</th>
<th>Initials</th>
<th>Signature</th>
<th>Start Date</th>
<th>End Date</th>
<th>PI Initials/Date</th>
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By initialing above, I, the PI, declare that during the conduct of the above study, I have delegated the following study-related activities:

**Responsibilities Legend**

1. Administer Consent  
2. Screen Subjects  
3. Obtain Medical History  
4. Perform Physical Exam  
5. Determine Eligibility  
6. Randomize Subjects  
7. Dispense Study Drug  
8. Drug Accountability  
9. Assess Adverse Events  
10. Complete Source Documents  
11. Complete Study Forms  
12. Provide Discharge Instructions  
13. Make Follow-up Phone Calls  
14. Query Management

Signature of Principal Investigator: ____________________________ Date: ___________
Current training certificates for all study team members

- Human Subject Protections (HSP)
- Good Clinical Practice (GCP)

https://www.citiprogram.org

https://hso.research.uiowa.edu
Training Documentation

- Documentation of study-related training, specific Study:
  - Procedures
  - Certifications
  - Protocol training

- Study specific procedure

- Electronic Data Entry

- Training for shipping biologics (IATA) Dangerous Goods Training

- Electronic data entry

- DOCUMENT THE TRAINING!!!

**Note: Be sure to have a process in place to check qualifications / credentials**
### Example Training Log:

**Training Log**

<table>
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<tr>
<th>Investigator Name</th>
<th>Protocol</th>
<th>Site Number</th>
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<th>Printed Name</th>
<th>Signature</th>
<th>Title of Training</th>
<th>Date of Training</th>
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**SAMPLE**
Screening/Enrollment Log

- Used to document the consent and screening of all subjects and the outcome of each screening
  - Contains subject’s assigned study code, date screened, eligibility for enrollment and/or reason for screen failure
  - **NO** subject identifiers
    - Tracked separately using a **Code List**
  - Follow site Screening and Enrollment Plan for enrolled subjects (as per IRB application)
  - May be paper or electronic
Subject Identification Code List

- Confidential List of trial subject names
  - Allows the Investigator/Institution to reveal identity of subject (ONLY)
  - NEVER share with outside entities (e.g. Sponsor, CRO)
Subject Visit Tracking Log

- Log of enrolled **Subject Visits**
- Used to track scheduled visits as per protocol **Target Visit Dates** (e.g. within visit windows)
- Reasons for **Early Termination (ET)**
- **Electronic Visit Log**: visit compliance with protocol-specific appointments/or procedure visit

**Example:**

![Target Visit Dates and Visit Windows Table]

- **Key**:
  - Window Open
  - Window Closed
  - Future Window

<table>
<thead>
<tr>
<th>Target Date</th>
<th>Visit Window</th>
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</thead>
<tbody>
<tr>
<td>12/29/2017</td>
<td>11/17/2017</td>
</tr>
<tr>
<td>10/30/2017</td>
<td>11/10-12/10</td>
</tr>
<tr>
<td>02/27/2018</td>
<td>02/27/2018</td>
</tr>
</tbody>
</table>
Investigational Product (IP) Accountability Records

- Documentation of IP delivery to the site, inventory at the site, use by each subject, return to site, return to sponsor or destruction
  - Shipment Records
  - Receipt documentation
  - Stock (inventory) Record
  - Subject Dispense Record
  - Temperature logs

- Investigational Drug Services (IDS) maintain records (e.g. study product is blinded to the research team)
  - Document location of records (e.g. Note-To-File in Reg Binder)
Clinical Laboratory Documentation

- Lab reference ranges
- Copy of lab certificates/accreditations (CAP, CLIA)
- PI determination of *clinical significance* for all lab reports along with PI signature/date
  - *i.e., clinically significant, nonsignificant, or abnormal*

Lab Specimen Tracking Log

- Specimen tracking log
- Shipping documentation
- Storage temperature logs
- Freezer inspection reports
Clinical Lab Certificates

Examples: UIHC Pathology CLIA/CAP

https://www.medicine.uiowa.edu/pathology/research/pathology-clinical-trials-support-core
**Adverse Events Documentation**

**Adverse Events (AEs) / Serious Adverse Events (SAEs)**
- SAE reporting forms and memos
- Correspondence, acknowledgement of reports of AEs
- Documentation that event was reported to IRB, Sponsor, regulatory authorities
- IND Safety Reports
- AE/SAE Log

**Unanticipated Problems (UPs) / AEs of Special Interest**
- Both UPs and AESI reports to IRB, Sponsor, FDA, and other regulatory authorities
Clinical Site Monitoring Visits

- Monitoring Signature Log/Visit Record

- Both Monitor and Research Team Member involved with the site visit must sign and date Visit Log:
  - Study Initiation Visit (SIV)
  - Interim Monitoring Visit (IMV)
  - Close-Out Visit

- File original letter/email announcing each visit

- File all visit correspondence

- Follow Up Letter or report documenting findings and action items

- Documentation that actions have been taken /issues have been resolved - signed off by monitor
Notes-To-File (NTFs)

- When used to document an issue in the conduct of the study or a discrepancy (e.g., missing data item or a missing date on a consent form) should include:
  - **Description** of the issue/discrepancy/or omission
  - **Root cause** for the issue/discrepancy/or omission
  - **Corrective and preventive actions** that have been taken to address the root cause

- Should be used “thoughtfully”
- When used properly a NTF can be a positive practice
- Document logistical problems or locations
- Document decisions made, instructions from the study sponsor, or problems experienced

Discrepancy or Problem → Action
Notes-To-File (NTFs)

- Print on institution letterhead
- Authored, signed, and dated by an individual responsible for its content:
  - **Principal Investigator (PI)** for issues/discrepancies/deviations related to PI responsibilities
    - e.g., *human subject protection or data integrity* at the site
  - **An appropriately credentialed individual from the sponsor** for issues/discrepancies/deviations related to actions taken by the sponsor/monitor
    - e.g., clarification of a protocol section
- If applicable, send a scanned pdf to a Data Management Center (DMC)
- File NTFs in the site Regulatory Binder
Deviation Log

- Used to document all protocol Deviations that occur on the study
- Deviations – changes, divergence, or departure from the approved study design or procedures of the research protocol that have not been approved by the IRB and Sponsor
- Report all Deviations to IRB and Sponsor as per requirements
Good Documentation Practice

- Document **what is** - and **what is not** – done
- Provide reasons for any missed information
- Use of indelible **blue** or **black** ink on paper forms.
  - Reduces fading over time or **smudging**
  - **No** pencils, felt-tipped markers or white-out
- No back or future dating – use of **current date** when entries are made
- No “ditto” marks for repetitive data
- Instrument printouts: Adhere printout to Original Source Document; add initials and date where the printout is attached.
- Printouts sent for research data purposes need **coded, redacted, or de-identified**
Good Documentation Practice
Correcting Information

- **Errors happen!** Corrections are expected
- Single **line through incorrect information**, do not obscure original data
- No writing over data (e.g. turning a 0 into a 9) - hides the original data
- Enter the **correct** information
- **Initial** and **date** when the **corrections** were made - **CAS 05/17/2018**
- Entries on study documents and changes to those entries should be made by study team members with the authority to do so as delegated by the PI
Good Documentation Practice

“ALCOA-C”

Attributable: to who created the record; sign & date

Legible: readable, clear, comprehensible, identifiable

Contemporaneous: record activity as events occur

Original: original source document

Accurate: exact, truthful, correct, verifiable date

Complete: capture all required data, no blank spaces

**Changes to source documents should be traceable.**
Electronic Documentation and Data

- **Electronic Medical Records (EMR)** present **security**, and other legal challenges; know your institutional regulations at UIHC.

- **Electronic Data Capture (EDC)** systems are being utilized for databases, electronic case report forms (eCRF), clinical monitoring, and maintaining regulatory documents. Examples: Medidata Rave, Oracle, InForm, OmniComm, RedCAP.

- **FDA guidance** (May 2016) for **source data** should be **ALCOA**.
Electronic Data

21 CFR 11 FDA regulations for Electronic Records; Electronic Signatures

- **Validate Systems** to ensure accuracy, reliability, consistent performance, ability to discern invalid or altered records
- **Access Controls**: Internal security safeguards limit access, passwords, authorized users, automatic times log off
- **External Security**: protect records
- **Audit Trails**: track all changes; date/time
- **Document** computer education, training and experience
Documentation Resources
Websites and Links for more information

▸ https://nccih.nih.gov/grants/toolbox#startup

▸ Register the Clinical Trial(s) https://www.clinicaltrials.gov


▸ University of Iowa Resources – Human Subjects Office & HAWKIRB: https://hso.research.uiowa.edu


▸ NIDCR’s Toolkit for Clinical Researchers: https://nidcr.nih.gov/research/toolkit

▸ Office for Human Research Protections (OHRP): https://www.hhs.gov/ohrp/


▸ https://nccih.nih.gov/grants/toolbox/pdfs
THANK YOU!