Setting yourself up for research documentation success: A regulatory binder journey

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Understand the importance of the regulatory binder in research

Learn how to address a problem should it arise

Strengthen your audit and QA review preparedness

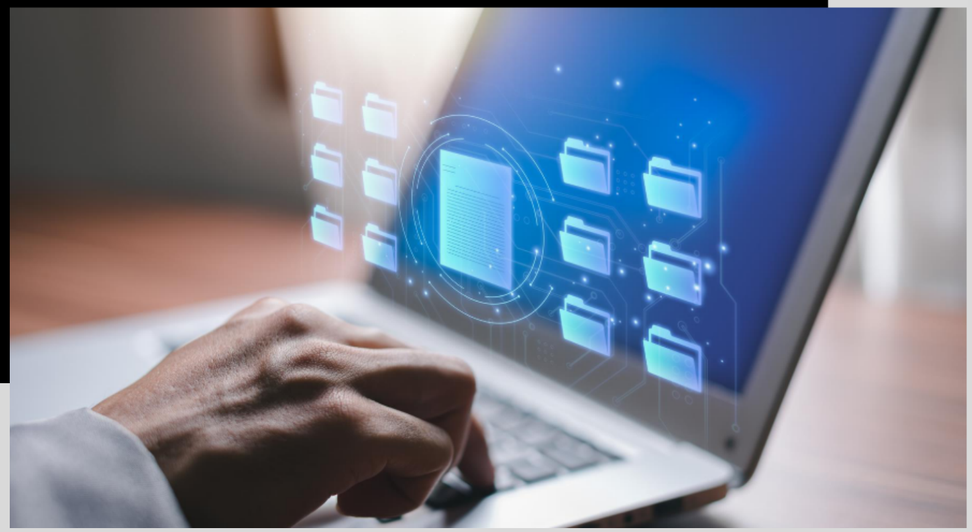
Key terms

Compliance
vs.
Misconduct

Quality
Control (QC)
vs.
Quality
Assurance (QA)

Monitoring
vs.
Auditing

Corrective Action
Plan (CAP)
vs.
Corrective and
Preventative
Action Plan
(CAPA)



"If it wasn't documented, it didn't happen"

ICH E6 (R3) II: 8, 9, and 10

ALCOA+ (ICH, FDA, HHS, WHO)

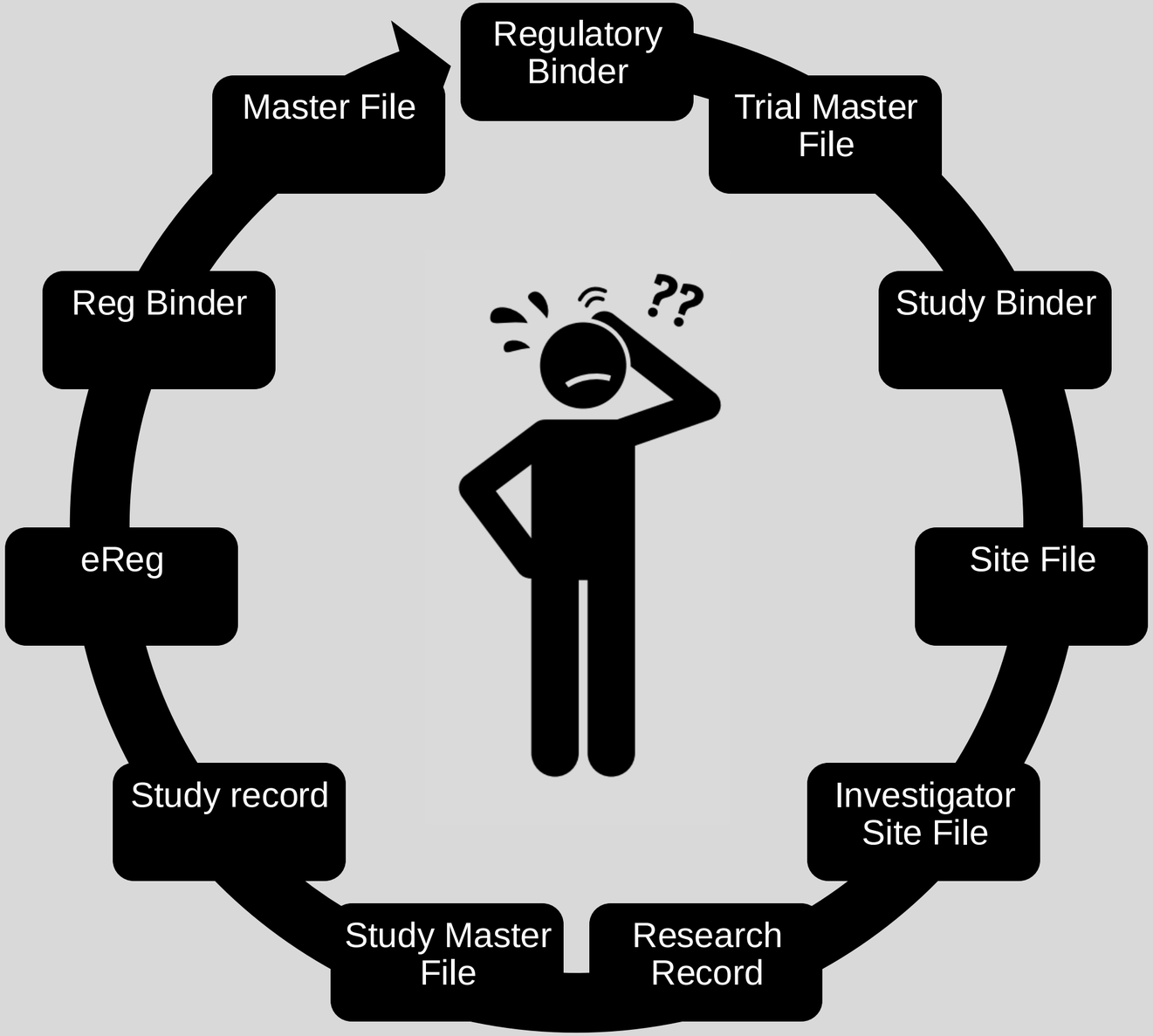
ICH E6 (R3) III: 2.12

Institution Specific Policies and Requirements

"If it wasn't documented, it didn't happen"

- Personally conduct or supervise the Human Research.
    - Protect the rights, safety, and welfare of participants involved in the research.
    - Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB, and in accordance with applicable federal regulations and local laws.
    - Assure that each participant is adequately informed and freely consents to participate in the in the research, unless a waiver of consent has been obtained from the UMB IRB. The Principal Investigator must personally assure that every reasonable precaution is taken to reduce risks to participants.
    - Delegate responsibility to the research staff in accordance with the staff's training and qualifications.
    - Assure that all procedures associated with the research are performed, with the appropriate level of supervision, only by individuals who are licensed or otherwise qualified to perform them under the laws of Maryland and polices of the University of Maryland, Baltimore.
    - Monitor the research study and perform quality management activities to ensure the protection of participants and the quality of the research data. Deficiencies identified during quality improvement processes must be addressed in a timely manner. Refer to "CHECKLIST: Investigator Quality Improvement Assessment" for more information.

Word Soup


Regulatory Binder
Trial Master File
Study Binder
Site File
Investigator Site File
Research Record
Study Master File
Study record
eReg
Reg Binder
Master File
??

Initiative to Standardize TMF

Clinical Data Interchange Standards Consortium

Cdisc.org

Resources Differ:
IIT vs. Industry Sponsored

Industry Sponsored	Principal Investigator	Funder
Provides Binder		x
Manages Binder	x	
Monitors Binder		x
QC/QA	x	x

Investigator Initiated	Principal Investigator	Funder
Provides Binder	x	
Manages Binder	x	
Monitors Binder	x	
QC/QA	x	

Start Strong!

Quality by Design (QbD) approach: ICH E6 (R3) III: 3.10

Contents (fixed and protocol dependent)

Table of Contents ESSENTIAL!

Clean, final binder PRIOR to enrollment/study start

MOP/SOPs to support protocol

Examples (UMSON) (Veeva)

Maintain!

QC (in every moment)
QA (risk-based frequency)

ICH E6 (R3) III: 3.11

Not just risk to participants
Think RECORD INTEGRITY!

Goal: Audit ready at all times

Maintain: Staff training and Management

-DoA log (signatures and initials)
-Study staff credentials (CVs/Licenses/professional trainings)
-Study staff general research training (CoI/PHS/GCP/HIPAA/Etc.)
-Study staff protocol specific training (log AND training materials)

Also... Consult your protocol/IRB application:
The PI will meet with the study coordinator(s) at least biweekly and more frequently as needed to discuss the progress and logistics of the study. The PI will meet with other study team members at a frequency that is decided upon initiation of their involvement, based on their individual role.

Maintain: Protocol Procedures

-Source documentation/CRF (align with any mods)
-Screening/enrollment log (eligibility source to back it up)
-Consent log (consent source to back it up)
-Participant payment log (documentation to back it up)
-Progress notes (participant binder)

Also... Consult your protocol/IRB application:
Participants who are enrolled will be provided a written copy of the consent form.

After a participant agrees to join the study, we will verbally ask the following questions to test their knowledge about the study.....

Participants will be compensated for their time with a $100 gift card or E-gift card and a parking voucher for that visit.

Maintain: Periodic Reviews & Data Mgmt

-IRB (submission, application, approval letter, communication)
- modifications
- RNI
- annual (if applicable)

-DSM reports (note: DSM is not the same as routine monitoring!)
-QA/Monitoring log (reports to back it up)

Also... Consult your protocol/IRB application:
Quality assurance reviews will be conducted monthly by the study coordinator and the resulting reports will be reviewed by the PI.

Are You Audit Ready?

Help is available

Forms are helpful

Prepare: Think like an Auditor

Regulatory Binder

Review for completeness/accuracy

-is the ToC and all tabs present and organized?
-are all contents present/accounted for?
-are all logs complete/current?
-are all IRB submission requirements met?

Review staff

-compare CICERO with DoA, trainings, CVs
-are trainings complete/documented? (protocol and general)

Participant Binder

Ex.

Sub ID 00X

Review data collected (ALCOA+)

-is it allowed per protocol?
-are there errors?
-outside of protocol window?
-typos?
-missing data?
-adverse events?
-was team member delegated to procedure?

Compare procedures with regulatory binder

-were the IRB approved forms used?
-were the IRB approved procedures followed?
-DSM
-consent forms/processes
-eligibility

What could go wrong?

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REPORTABLE NEW INFORMATION

Please post this prominently in your research or office space.

Report the information items that fall into one or more of the following categories to the IRB within 5 business days using this form:

Information that does not fall under any of the categories does not require reporting to the IRB.

1) Information that indicates a new or increased risk. For example:
   a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
   b. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk.
   c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
   d. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.
   e. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.
   f. Any changes significantly affecting the conduct of the research.
2) Any harm experienced by a subject or other individual which in the opinion of the local investigator is **unexpected** and at least **probably related** to the Human Research procedures and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.
   a. A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
   b. A harm is "a least probably related to the Human Research procedures" if in the opinion of the local investigator, the research procedures more likely than not caused the harm (greater than 50% probability).
3) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
4) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
5) Breach of confidentiality.
6) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
7) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
8) Complaint of a subject that cannot be resolved by the research team.
9) Suspension or termination of the research by the sponsor or the investigator.
10) Unanticipated adverse device effect (Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).
11) Audit, inspection, or inquiry by a federal agency.
12) Written reports of study monitors.
13) For Veterans Administration (VA) research only: any local or internal serious adverse event or serious problem that is both unanticipated and related to the research.
14) Determination from IRB of Record for continuing non-compliance, serious non- compliance, serious & continuing non-compliance, unanticipated problem, suspension or termination at UMB (External IRB studies ONLY).
15) RNI submission for OAC, HRPO & VA R&D Use only
16) Research Resumption Plan during COVID-19 pandemic

How Do I Document a Problem?

- **Deviation Log**
- **AE Log**
- **QA Report**
- **RNI**
- **NTF not ideal**

CAP or CAPA

Report It

Revisit QbD (Mod needed?)

Learn from mistakes/past/others

How do I fix it?

Close it up!

DoA

Retention/destruction

References and Resources

- https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf
- https://www.umaryland.edu/hrp/for-researchers/investigator-manual/
- https://www.umaryland.edu/media/umb/oaa/hrp/documents/study-tools-docs/HRP-105---Reportable-New-Information.pdf
- https://www.nursing.umaryland.edu/research/resources/regulatory-affairs/researcher-toolkit/
- https://www.cdisc.org/standards/trial-master-file-reference-model
- https://sites.veevavault.help/gr/sitevault/getting-started/ebinder-card/
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/corrective-and-preventive-actions-capa
- https://www.gmp-compliance.org/gmp-news/alcoa-what-does-it-mean
- https://www.who.int/publications/m/item/annex-4-trs-1033

Thanks! Questions?

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