A Primer on the Regulatory Binder:

How to Set up and Maintain Regulatory Documentation to Meet the Needs of Your Research

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Objectives

- Describe why there is a need to maintain regulatory documentation for your research study
- Define regulatory binder and describe its purpose
- List the essential documents needed to demonstrate compliance with regulatory requirements
- Demonstrate how to use the tools and templates offered by the CRRO to maintain this documentation

ICH GCP

- GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected... And that clinical trial data are credible.

- The objective …. to facilitate mutual acceptance of clinical data by regulatory authorities … (US, EU, Japan)

FDA Guidance, Feb 2018, E6(R2) GCP: Integrated Addendum to ICH E6(R1)

More on GCP

- To the extent possible, the principles of GCP should generally apply to all clinical research involving human subjects, and not just research involving pharmaceutical or other medical products.

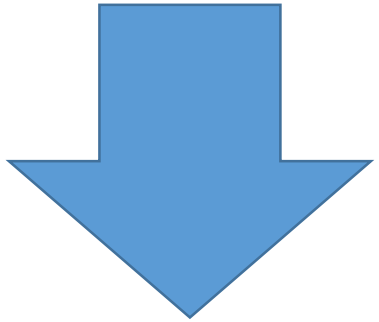
- Although some principles of GCP may not apply to all types of research on human subjects, consideration of these principles is strongly encouraged wherever applicable as a means of ensuring the ethical, methodologically sound and accurate conduct of human subject's research.

Handbook for Good Clinical Practice, WHO, 2002

“Essential Documents”

- “Individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.”
  - Demonstrate compliance of the investigator, sponsor and monitor
  - Demonstrate compliance with GCP and/[or] applicable regulatory requirements

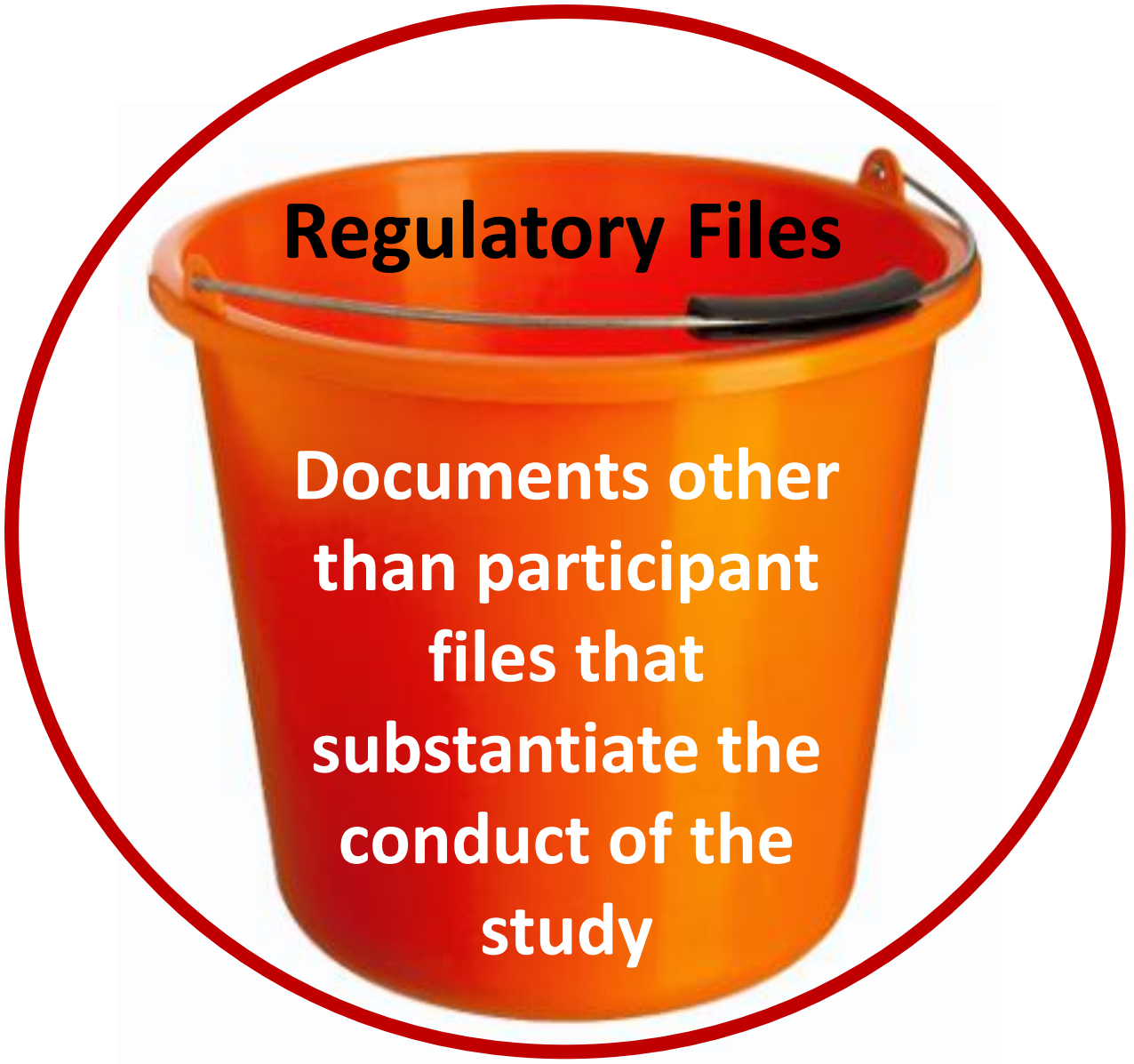
ICH GCP 8.1



Can we rely on these results to answer the study question?

Can we rely on these results to **change practice**?

2 Buckets of Essential Documents



DATA is the product of your study …..

Your study data supports the study hypothesis ….

You publish articles in medical journals on the basis of your data …..

Your data contributes to changing practice …..

What supports your data?


AAA!
We d
everythi
PERF CTLY!
The BEST
Scientific Study
EVER!!!!

How does regulatory documentation support your data?

A few (of many) examples….	
Study involves complex cognitive testing as main outcome measure	Show that testers were trained and qualified to do the testing (training records and CVs); and delegated
Study has three protocol versions with major amendments for each	Show that the investigator was informed of the new versions AND that the IRB approved all of them
Study uses outside laboratories for diagnostic testing	Show that the laboratories met required standards for processing diagnostic samples
Study involves high risk intervention, and complex clinical procedures and follow-up	Show that the staff assigned the responsibilities (such as clinical follow up and informed consent) are qualified and have been delegated by the PI
The study is under and Investigator-held IND	Show that the PI met his/her responsibilities regarding FDA reporting
Study involves investigational new drug	Show that drug was shipped, stored and used according to protocol

Investigator Responsibilities: *Telling the Story*

ICH GCP 1.34; 4.0-4.13; 21 CFR 312.60 and 812.110; FDA Guidance Investigator Responsibilities, Oct. 2009

- Personally conduct or supervise the investigation
- Appropriate delegation of tasks
- Comply with protocol: Ensure study is conducting according to the investigational plan, applicable regs, policy, guidance
- Properly inform subjects
- Read and understand protocol and interventions
- Preparation and maintenance of case histories of participants (documentation)
- File appropriate reports (deviations, safety, financial disclosures, progress reports, study closure, etc.)
- Appropriate record-keeping and retention
- Compliance with IRB review
- Control and Accountability of the investigational items
- Appropriate record-keeping and retention
- Permit monitoring and auditing

Sponsor Responsibilities: *Telling the Story*

See ICH GCP 5.0 – 5.23; 21 CFR 312 Subpart D; 21 CFR 812.100

- Selecting qualified investigators and obtaining/maintaining appropriate documentation to support their qualifications.
- Control and Accountability of the investigational items
- Ensuring proper monitoring/selection of monitors
- Providing investigators with the info they need to conduct an investigation properly
- Monitor progress of study and inform investigators and FDA of significant new adverse effects
- Assuring that the study is conducted in accordance with the plan
- Appropriate record-keeping and retention
- Readiness for audit
- Maintain an effective IND or IDE
- Trial Registration

What is a Regulatory Binder?

- Purpose is to organize and maintain documents required by regulations
  - A method of organizing this complex set of regulatory documents
- Typically organized by sections following ICH GCP Section 8.0: *Essential Documents*
- Should be accessible by regulatory authorities, IRB, institutional QA, etc.
- Enables evaluation of study conduct and quality of data

The Regulatory Binder will be monitored/audited to:

- Confirm validity of study/trial conduct
- Confirm integrity of data collected

ICH GCP 8.1

Regulatory Binder…. AKA…

- Investigator binder
- Study binder
- Regulatory files
- Study files
- Investigator study files
- Regulatory documentation
- Essential documents
- Trial Master File (TMF)

Regulatory Binder doesn't have to be a binder

- Multiple notebooks and/or files
  - Organized by type/purpose of documents
  - Can be located in multiple locations/formats
    - i.e. IRB approvals in INSPIR
  - None, part, or all can be electronic

- You will be accessing it a lot; make sure it's easily retrievable!

A *Sampling* of Regulatory Essential Documents (ICH GCP 8.0)

- Staff training
- Signature/ Delegation log
- Investigator's brochure/package insert
- Protocol and revisions (including materials to be given to study participants, i.e. recruitment…)
- Informed consent forms (unsigned clean-copies, all versions)
- Case Report Forms/Data Collection forms (clean-copies, all versions)
- IRB submissions
- Regulatory authorizations
- Lab normal ranges and updates
- CVs for investigators
- Medical/lab/technical procedures (qual. control, etc.)
- Sample labels for investigational product and instructions for handling
- Shipping records
- Decoding procedures for blinded trials
- Master rx list
- Monitoring reports
- Subject screening/enrollment logs
- 1572 forms/Investigator Agreement
- Safety notifications from Sponsor

ICH GCP Section 8: Essential Documents for the Conduct of a Clinical Trial

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT** – **INFORMED CONSENT FORM** (including all applicable translations)	To document the informed consent	X	X
	– **ANY OTHER WRITTEN INFORMATION**	To document that s given appropriate w information (conter to support their abil informed consent		
	– **ADVERTISEMENT FOR SUBJECT RECRUITMENT** (if used)	To document that r measures are appro coercive		

52

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** – Protocol/amendment(s) and CRF – Informed consent form – Any other written information provided to subjects – Advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	
8.3.3	**DATED, DOCUMENTED APPROVAL/FAVORABLE OPINION OF INSTITUTIONAL REVIEW BOARD IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** • Protocol amendment(s) • Revision(s) of: — Informed consent form — Any other written information to be provided to the subject — Advertisement for subject recruitment (if used) • Any other documents given approval/favorable opinion • Continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s).	X	

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X

ICH GCP Guidelines (See section 8 "*Essential Documents for the Conduct of a Clinical Trial*")

https://www.fda.gov/media/93884/download

What research is required to keep a Regulatory Binder?

- Any clinical study that follows ICH GCP
- Some NIH institutes require a regulatory binder for clinical trials and intervention studies
- FDA-regulated research…
  - Although FDA regulations do not use the terms “essential documents” or “regulatory binder,” the ICH GCP guidance (which does) is formal FDA guidance. Also, the FDA regulations do describe many requirements; the only way to demonstrate compliance is through keeping “essential documents”
- Any study that wants to demonstrate compliance with the regulations and was conducted to high quality standards

Whose responsibility is the binder?

- The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial….

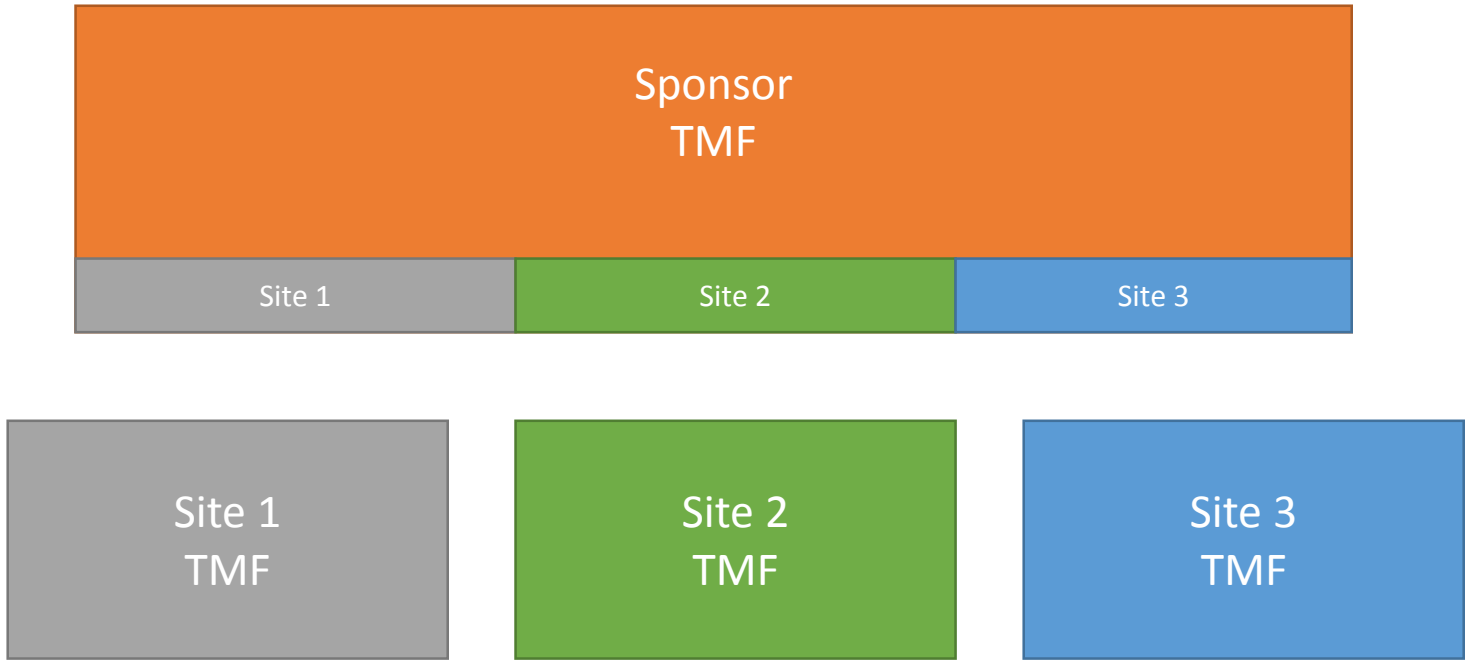
  ICH GCP 4.9.4 Records and Reports

  - This is often delegated to study staff….

- The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial….

  ICH GCP 5.5.6 Trial Management, Data Handling, and Recordkeeping

Multicenter trial



How do I Create a Regulatory Binder for My Study?

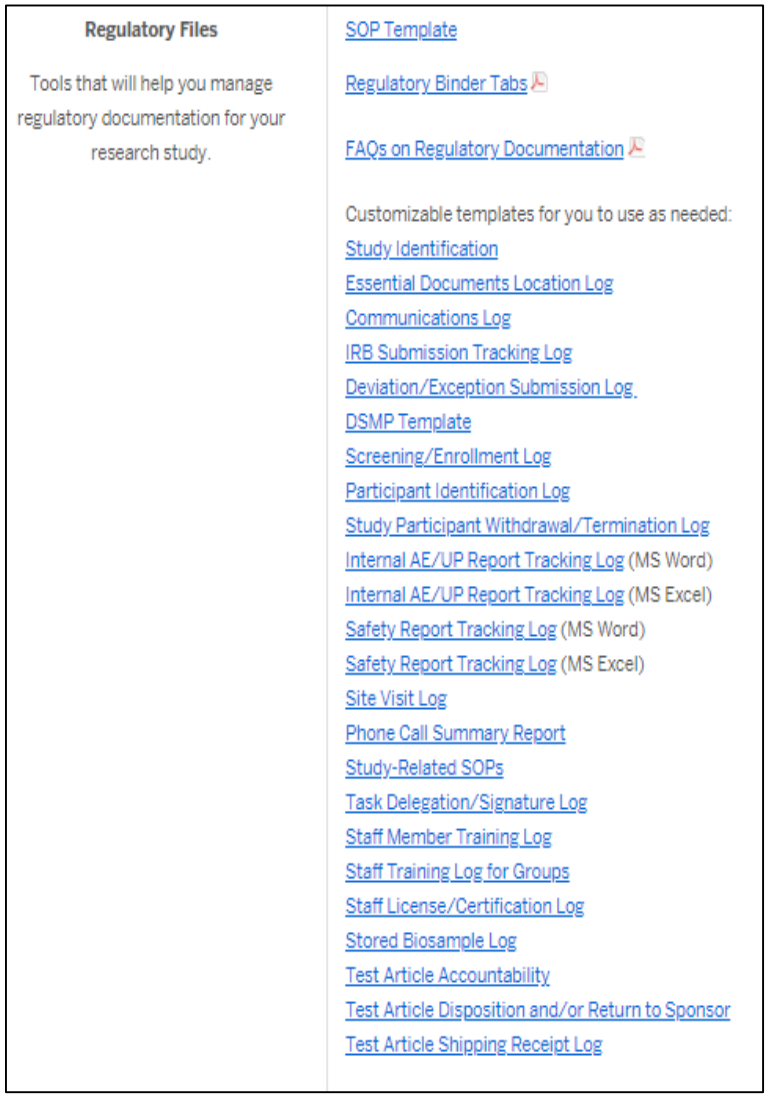
1. Don’t reinvent the wheel!

- Use the binder tabs/guidance supplied by the Sponsor, if applicable

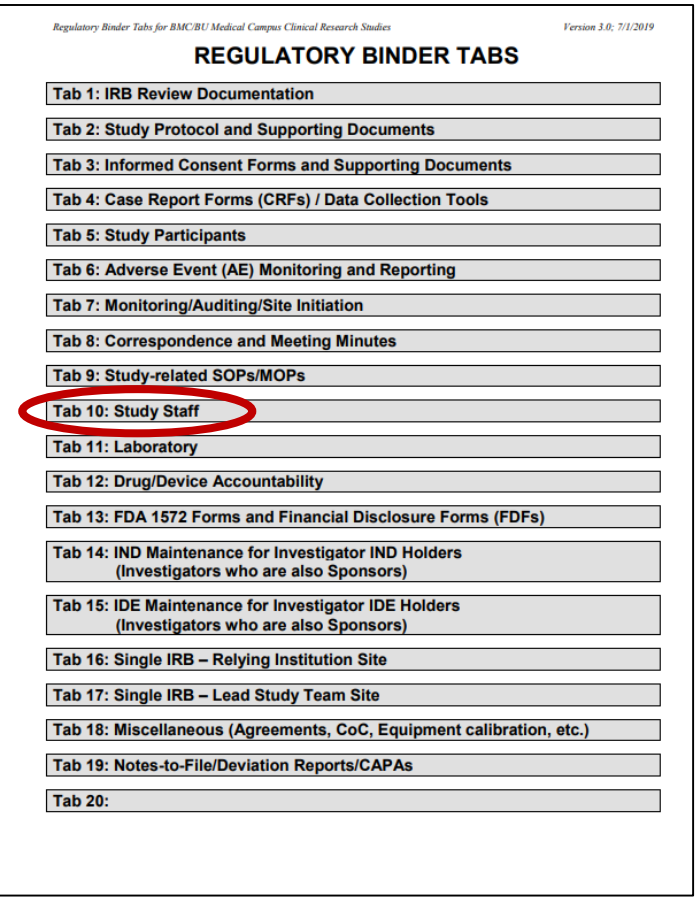
- Use the binder tabs/guidance supplied by the CRRO!

http://www.bumc.bu.edu/crro/

  - Click on Resources then Study Documentation Tools
  - Scroll to Regulatory Files for:
    - Regulatory Binder tabs
    - FAQs on Regulatory Documentation
    - 24 Customizable templates



Anatomy of a Binder Tab



Regulatory Binder Tabs for BMC/BU Medical Campus Clinical Research Studies *Version 3.0; 7/1/2019*

REGULATORY BINDER TABS

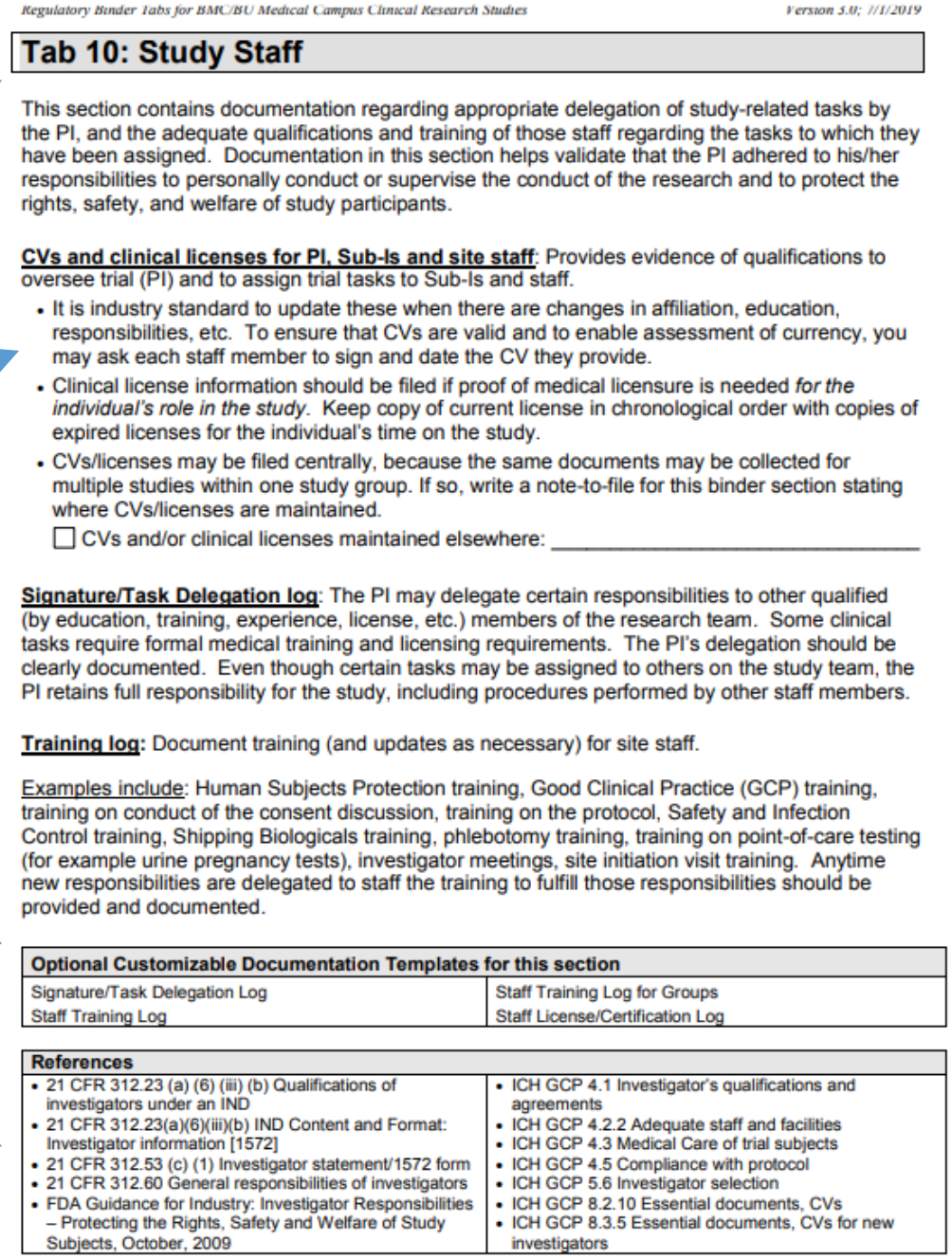
- Tab 1: IRB Review Documentation
- Tab 2: Study Protocol and Supporting Documents
- Tab 3: Informed Consent Forms and Supporting Documents
- Tab 4: Case Report Forms (CRFs) / Data Collection Tools
- Tab 5: Study Participants
- Tab 6: Adverse Event (AE) Monitoring and Reporting
- Tab 7: Monitoring/Auditing/Site Initiation
- Tab 8: Correspondence and Meeting Minutes
- Tab 9: Study-related SOPs/MOPs
- Tab 10: Study Staff
- Tab 11: Laboratory
- Tab 12: Drug/Device Accountability
- Tab 13: FDA 1572 Forms and Financial Disclosure Forms (FDFs)
- Tab 14: IND Maintenance for Investigator IND Holders (Investigators who are also Sponsors)
- Tab 15: IDE Maintenance for Investigator IDE Holders (Investigators who are also Sponsors)
- Tab 16: Single IRB – Relying Institution Site
- Tab 17: Single IRB – Lead Study Team Site
- Tab 18: Miscellaneous (Agreements, CoC, Equipment calibration, etc.)
- Tab 19: Notes-to-File/Deviation Reports/CAPAs
- Tab 20:

Title/Tab#

Guidance

Templates

Regulatory references



Regulatory Binder Tabs for BMC/BU Medical Campus Clinical Research Studies *Version 3.0; //1/2019*

Tab 10: Study Staff

This section contains documentation regarding appropriate delegation of study-related tasks by the PI, and the adequate qualifications and training of those staff regarding the tasks to which they have been assigned. Documentation in this section helps validate that the PI adhered to his/her responsibilities to personally conduct or supervise the conduct of the research and to protect the rights, safety, and welfare of study participants.

CVs and clinical licenses for PI, Sub-Is and site staff: Provides evidence of qualifications to oversee trial (PI) and to assign trial tasks to Sub-Is and staff.

- It is industry standard to update these when there are changes in affiliation, education, responsibilities, etc. To ensure that CVs are valid and to enable assessment of currency, you may ask each staff member to sign and date the CV they provide.
- Clinical license information should be filed if proof of medical licensure is needed *for the individual's role in the study*. Keep copy of current license in chronological order with copies of expired licenses for the individual's time on the study.
- CVs/licenses may be filed centrally, because the same documents may be collected for multiple studies within one study group. If so, write a note-to-file for this binder section stating where CVs/licenses are maintained.
  - ☐ CVs and/or clinical licenses maintained elsewhere: _____

Signature/Task Delegation log: The PI may delegate certain responsibilities to other qualified (by education, training, experience, license, etc.) members of the research team. Some clinical tasks require formal medical training and licensing requirements. The PI's delegation should be clearly documented. Even though certain tasks may be assigned to others on the study team, the PI retains full responsibility for the study, including procedures performed by other staff members.

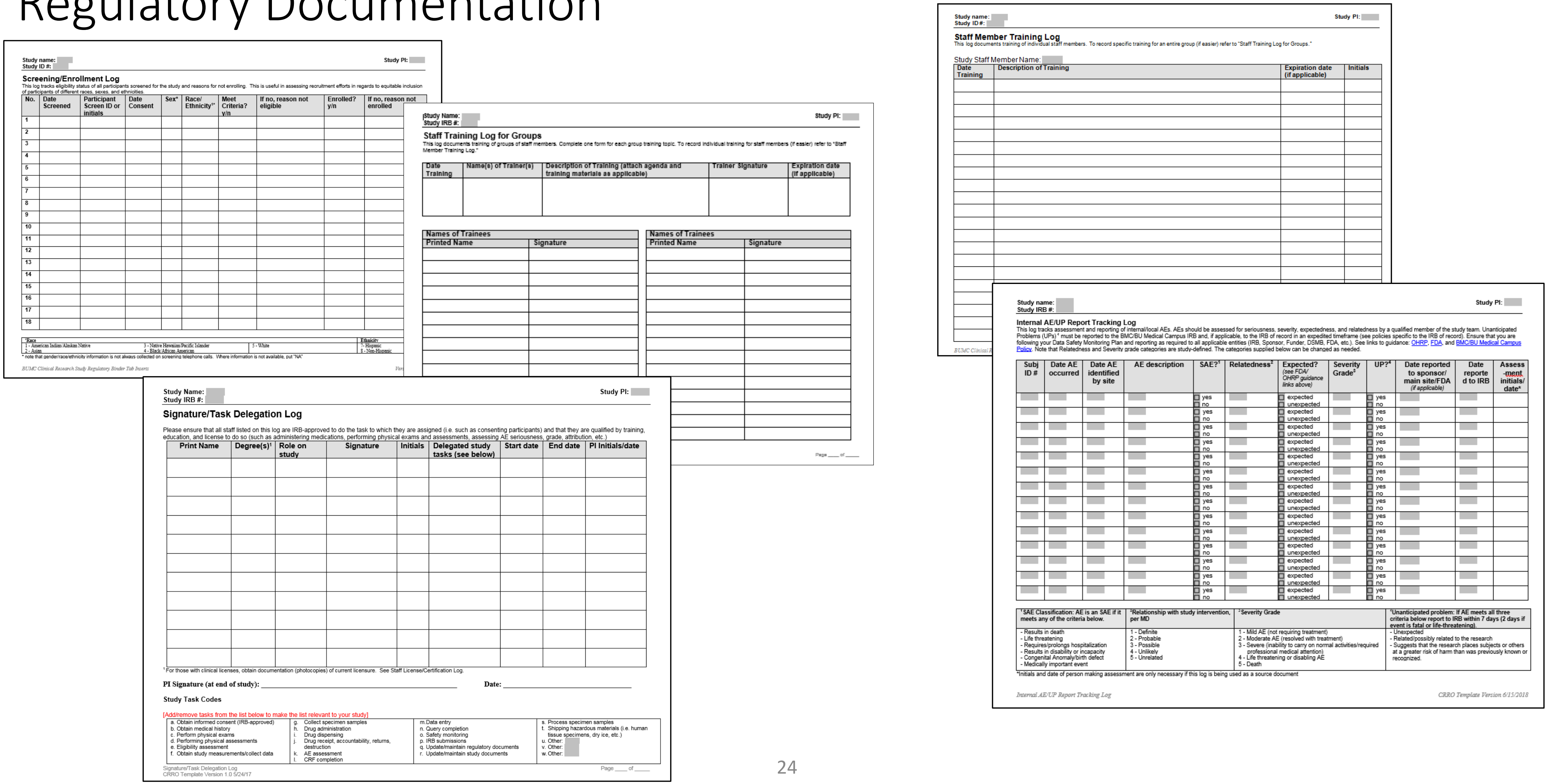
Training log: Document training (and updates as necessary) for site staff.

Examples include: Human Subjects Protection training, Good Clinical Practice (GCP) training, training on conduct of the consent discussion, training on the protocol, Safety and Infection Control training, Shipping Biologicals training, phlebotomy training, training on point-of-care testing (for example urine pregnancy tests), investigator meetings, site initiation visit training. Anytime new responsibilities are delegated to staff the training to fulfill those responsibilities should be provided and documented.

Optional Customizable Documentation Templates for this section	
Signature/Task Delegation Log	Staff Training Log for Groups
Staff Training Log	Staff License/Certification Log

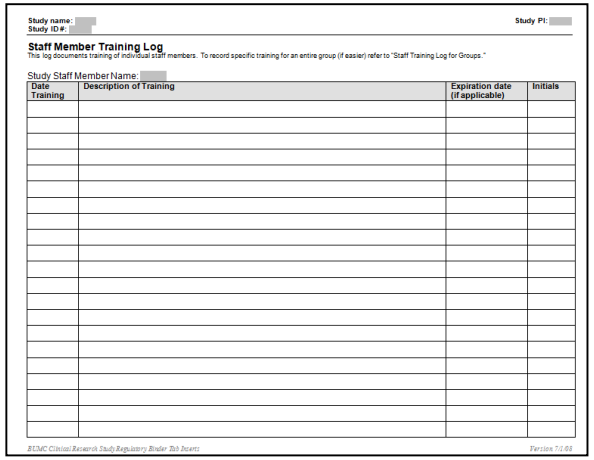
References	
• 21 CFR 312.23 (a) (6) (iii) (b) Qualifications of investigators under an IND	• ICH GCP 4.1 Investigator's qualifications and agreements
• 21 CFR 312.23(a)(6)(iii)(b) IND Content and Format: Investigator information [1572]	• ICH GCP 4.2.2 Adequate staff and facilities
• 21 CFR 312.53 (c) (1) Investigator statement/1572 form	• ICH GCP 4.3 Medical Care of trial subjects
• 21 CFR 312.60 General responsibilities of investigators	• ICH GCP 4.5 Compliance with protocol
• FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects, October, 2009	• ICH GCP 5.6 Investigator selection
	• ICH GCP 8.2.10 Essential documents, CVs
	• ICH GCP 8.3.5 Essential documents, CVs for new investigators

A Sampling: CRRO Templates to Assist you in Your Regulatory Documentation



Logs for just about Any Study: Staff Delegation Log and Training Log

- Demonstrates appropriate investigator oversight
- Shows that study-related tasks have been delegated appropriately.
- Appropriate training documented for those performing study-related tasks shows individuals are qualified to take on their delegated role(s).



Study name:
Study ID #:
Study PI:

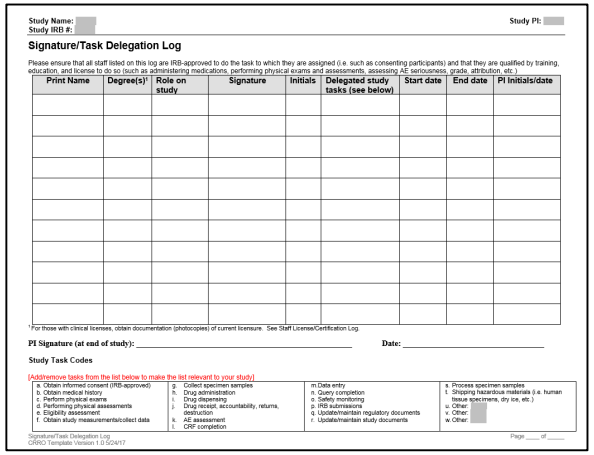
Staff Member Training Log

This log documents training of individual staff members. To record specific training for an entire group (if easier) refer to "Staff Training Log for Groups."

Study Staff Member Name:

Date Training	Description of Training	Expiration date (if applicable)	Initials

BUMC Clinical Research Study Regulatory Binder Tab Inserts *Version 7.1.03*



Study Name:
Study IRB #:
Study PI:

Signature/Task Delegation Log

Please ensure that all staff listed on this log are IRB-approved to do the task to which they are assigned (i.e. such as consenting participants) and that they are qualified by training, education, and license to do so (such as administering medications, performing physical exams and assessments, assessing AE seriousness, grade, attribution, etc.).

Print Name	Degree(s)[1]	Role on study	Signature	Initials	Delegated study tasks (see below)	Start date	End date	PI initials/date

[1] For those with clinical licenses, obtain documentation (photocopies) of current licensure. See Staff License/Certification Log.

PI Signature (at end of study): _____ **Date:** _____

Study Task Codes

[Add/remove tasks from the list below to make the list relevant to your study]

a. Obtain informed consent (IRB-approved) b. Obtain medical history c. Perform physical exams d. Performing physical assessments e. Eligibility assessment f. Obtain study measurements/collect data	g. Collect specimen samples h. Drug administration i. Drug dispensing j. Drug receipt, accountability, returns, destruction k. AE assessment l. CRF completion	m.Data entry n. Query completion o. Safety monitoring p. IRB submissions q. Update/maintain regulatory documents r. Update/maintain study documents	s. Process specimen samples t. Shipping hazardous materials (i.e. human tissue specimens, dry ice, etc.) u. Other: v. Other: w.Other:

Signature/Task Delegation Log
CRRO Template Version 1.0 5/24/17

Page ____ of _____

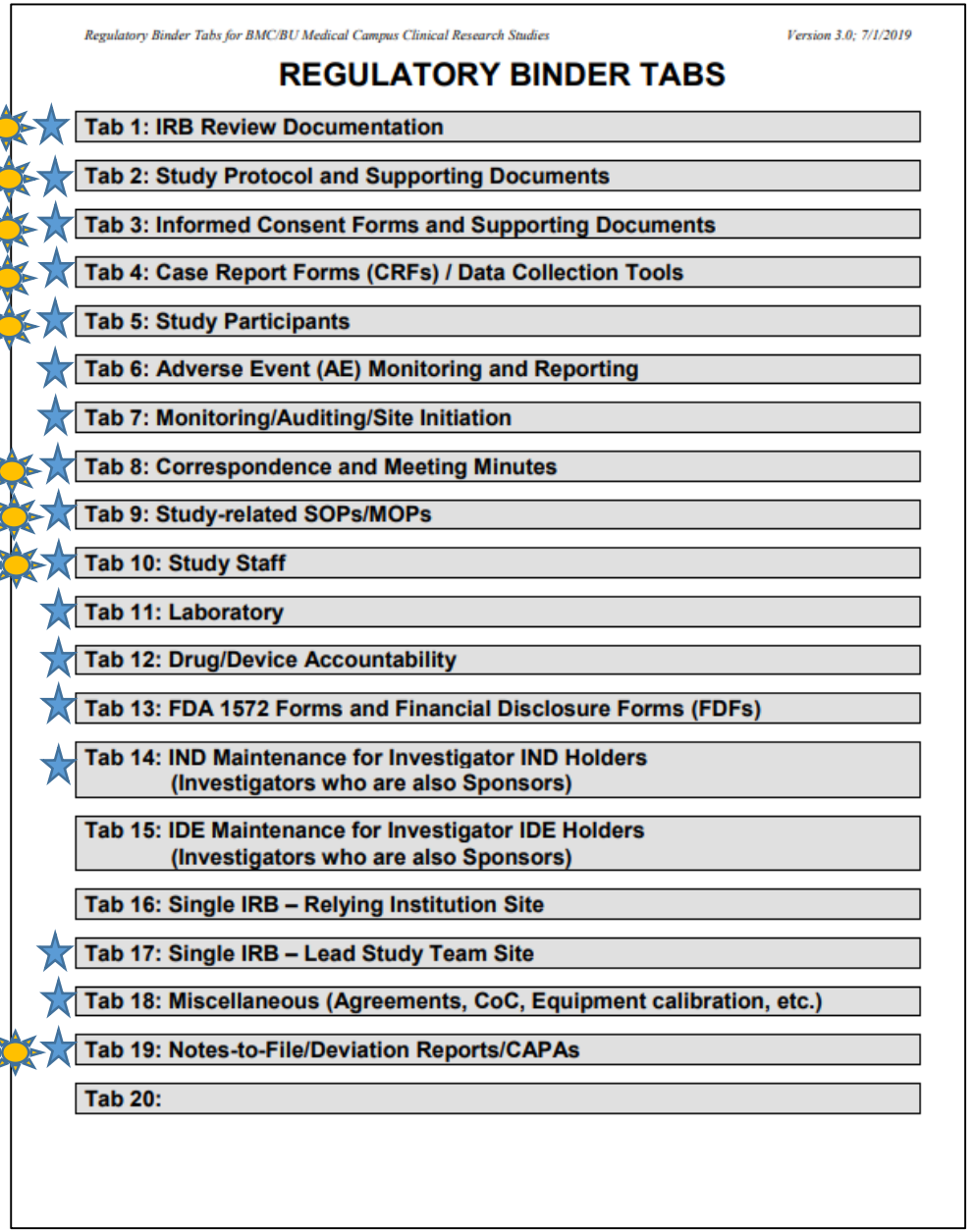
2. Ask yourself: Is my study “Delux” or “Basic”?

Delux:

- Investigator-initiated multicenter drug study
- Investigator holds IND
- Using Single IRB
- Laboratory testing

Basic:

- Single center mixed methods study
- Survey and data collection from the EMR



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Considerations for developing your regulatory binder

- Testing a drug or device?
- FDA regulated *and* under an IND or IDE?
  - Is your PI the Sponsor-Investigator? (i.e. holds the IND or IDE)
- Is your site also the main site of a multicenter study?
- Are you enrolling subjects (as opposed to just collecting EMR data)
- Do you utilize a laboratory?
- Does your study utilize a single IRB?
- Industry sponsored?

Going Electric?

- In the current hardcopy system, flexibility to store documents that are already in electronic format (i.e. INSPIR documents)
- Some use a “hybrid” version where hardcopy documents are signed, scanned, uploaded to an electronic file management system
- A fully electronic system will require electronically capturing 21 CFR part 11 compliant signatures
  - Off the shelf systems
  - Custom-built systems

H. Seifert. A Case Study in Redefining Regulatory Binder Management, 4/17, Clinical Researcher
https://acrpnet.org/2017/04/01/case-study-redefining-regulatory-binder-management/

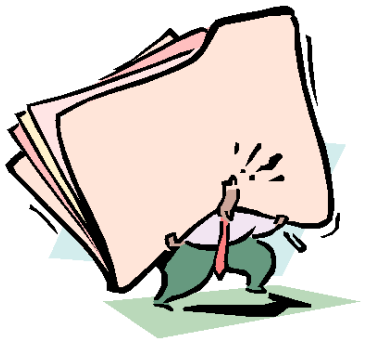
Common Findings on QA Reviews

- No method for organizing/maintaining regulatory files
- Delegation log not updated with new staff
- Delegation log doesn't show the PI has delegated some of tasks the coordinator is doing
- Training logs incomplete or not updated
- Lack of consistency (ex: indiv. is on the delegation but not training log)
- FDA reporting records not easily retrievable and not organized (i.e. Safety Reports, Annual Reports, etc.)
- Training on major protocol changes not documented

“Binder-doooos”

- Consider your study:
  - Plan your binder based on regulatory requirements
  - Do you have an industry sponsor (who has its own requirements)…
- Develop a system of organizing study files that works for you
  - It should be able to be understood and used by someone who doesn’t know your study
- Begin your binder before the start of the study
  - Before IRB approval and recruitment begins
  - Continue to update the binder contents throughout the life of the study to close-out

“Binder-dooos”



- If divided into several binders (or file cabinets, etc.) in different locations, the main binder should list location of all documents
- Make sure the entire team knows where this documentation is
  - It’s an important reference that may be needed when you least expect it!
- It’s a changing collection of documents – keep the binder updated
  - Don’t wait for an audit notification to collect your documentation
- NEVER discard outdated versions of documents
- Make sure you comply with your data retention and destruction processes!
- Make sure you appropriately store and secure records as described in your IRB application and the study protocol
- Make sure you make records available to monitors/auditors

“Binder-doooos”

- Develop a Written process (SOP) for Regulatory Documentation Oversight/Updating
  - Designate study staff to maintain the binder
  - Ensure staff are trained on binder SOP
  - Designate a safe, secure storage area for binders/files
  - Specify how long records will be retained for the study
  - Describe data storage and destruction processes
  - Build into the process a regular internal “self-QA review” of the binder

Helpful guidance

- CRRO Regulatory Binder Tabs, FAQs, and Templates http://www.bumc.bu.edu/crro/tools/
- Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects, FDA Guidance 2009 https://www.fda.gov/media/77765/download
- FDA Inspections of Clinical Investigators https://www.fda.gov/media/75185/download
- U.S. FDA Guidance – Q&A Form FDA 1572 (May 2010) https://www.fda.gov/media/78830/download
- DIA Trial Master File TMF Reference Model
- ICH GCP Guidelines (See section 8 "*Essential Documents for the Conduct of a Clinical Trial*") https://www.fda.gov/media/93884/download

Thank you!