CASE WESTERN RESERVE UNIVERSITY

CWRU HRPP REGULATORY BINDER

December 2024

Per the Case Western Reserve University Investigator Manual, one of the responsibilities of a study's Principal Investigator is the creation and maintenance of a Protocol File, also known as a Regulatory Binder. **A Regulatory Binder is required for <u>all research</u> that is determined to be engaged in Human Subjects Research including Exempt, Expedited, and Full Board protocols.**

While the task of creating and maintaining a Regulatory Binder can be delegated to a study team member, ultimate responsibility remains that of the Principal Investigator. **For more information, see the Investigator Manual, Chapter 6 – Principal Investigator and Study Team Members Responsibilities, Item 10.**
Investigator Manual- AAHRPP Version 12.04.2023.pdf (case.edu)

The purpose of a Regulatory Binder is to organize a study's essential documents in one location. The binder should (a) provide a comprehensive overview of the entire study, (b) act as a resource for study team members to readily access documents, and (c) be easily understood by someone who is not familiar with the study.

The following pages include an Index for the Study Regulatory Binder, templates, and recommendations for storage and maintenance. For additional information, see NIH Chapter 7 - Conducting Your Study (nih.gov)

In general, these items are required or recommended based on federal regulations and guidelines:

Items	Examples
Study Team Qualifications	Signed and dated CVs or resumes for all team members, including PIs, Co-Is, and staff; professional licenses; CREC and GCP certification
Training Records	Documentation, in the form of a log and/or reports, of all study-related staff training with dates and signatures
Delegation of Responsibility	Log of the study-related procedures delegated to each study team member by the Principal Investigator, with signatures and initials
Contact Information	Phone numbers, email addresses, and business mailing addresses of each study team member in order of responsibility (PI, Co-I, project/lab manager or coordinator, assistants, students)
Grant Award, Funding Agreement, Scope of Work Documents, Data Use Agreements	All completed grant award, funding agreement, scope of work, data use, and sponsor contract documents, including modifications, renewals, and sponsor correspondence
IRB-Approved Protocol and Modifications	Numbered and dated versions of the approved study protocol and all IRB correspondence
IRB-Approved Informed Consent, Assent, and/or Information Forms	Numbered and dated versions of the approved consent form(s)
Recruitment Materials	IRB content-approved flyers, advertisements, letters
Blank Data Collection Instruments	Word or PDF versions of study data collection surveys, questionnaires, scales, and interview scripts

Screening Log	A de-identified log of all potential participants who have been contacted, screened, or pre-screened for the study; include reasons for screen failures (ineligible) and declined to participate
Enrollment Log	A log of all enrolled participants who have consented to the study and their Participant/Subject IDs; include withdrawal and study completion information. Also, if the study design includes multiple arms, include arm allocation and blinding (if applicable) information.
Reportable New Information Logs (Adverse Event, Protocol Deviation, Unanticipated Problem Logs)	Documentation of Participant Complaints, Adverse Events, Protocol Deviations, and Unanticipated Problems including RNI submissions and their outcome
Data Safety and Monitoring Documents	DSMB reports (if applicable) and/or log and reports of any data safety and monitoring performed by study team members or independent monitors
The following items contain Applicable/Not Applicable notes	
Laboratory Certification and Laboratory Normal/Reference Ranges	IF APPLICABLE copies of CLIA certifications, normal laboratory and reference values and manuals, lab director's CV; if NOT APPLICABLE, include a note that no laboratories or laboratory tests are used for the study
Investigator's Brochure or Package Inserts	IF APPLICABLE the package insert (for an approved drug), Investigator Brochure (IB), or device manual; if NOT APPLICABLE, include a note that no drugs or devices are used for the study
Drug or Device Accountability Records	IF APPLICABLE dispensing log, shipping and receiving records, randomization/blinding plans, return/destruction, temperature monitoring logs/reports, text of labels attached to investigational products; if NOT APPLICABLE, include a note that no drugs or devices are utilized for the study
FDA Documents	IF APPLICABLE form 1572, FDA correspondence, annual IND reports, and IND Safety Reports; if NOT APPLICABLE, include a note that the study is not (a) FDA funded or (b) that no FDA-regulated drugs or devices are utilized for the study
Specimen Tracking Log	IF APPLICABLE a log of research specimens including type of specimen, storage purpose and location, link to participant ID number, consent for future use; if NOT APPLICABLE include a note that no specimens were collected or stored for this study
Site Monitoring Log	IF APPLICABLE (for studies with outside monitors, such as multisite studies) a log for monitors to document their visits, visit correspondence; if NOT APPLICABLE include a note that no outside monitoring is being conducted for this study

Binder Setup and Maintenance

Regulatory Binders can be either hard copy, in the form of a physical ring binder with index tabs, or stored electronically in a secure environment, such as CWRU Box, with subfolders representing tabs. A sample of tabs for a physical binder or folder/subfolder names for an electronic binder is included below. Updates of the binder should occur contemporaneously, as new information and updated documents become available.

NOTE: It is important to retain all documentation; DO NOT replace an older document version with a new version or discard outdated documents. Documents should be filed in reverse chronological order. If the binder is electronic, this can be accomplished by creating additional subfolders to file outdated or expired documents (recommended) or by adding dates to the document names.

REGULATORY BINDER

1. **CONTACT INFORMATION**: document(s) with study team member contact information including names and study roles, phone numbers, emails, and office mailing addresses. This can be in the form of a list, organizational chart, phone tree, or other comprehensive documentation.

2. **CREDENTIALS and TRAINING**
   - **2.1 CVs**: current curricula vitae (CVs), resumes, and/or biosketches for each study team member, signed and dated, updated every 2 years. You may also create an additional subfolder here (subfolder 2.1a) to store outdated versions of the CVs and prevent confusion as to which is the most recent/current version (e.g., Outdated CVs, Old CVs-Do Not Use).
   - **2.2 Certifications and Licensures**
     - **2.2a. CREC**: include here the CREC Certificates for each study team member. As CREC Certificates expire, upload a current version while retaining expired certificates. You may also create additional subfolders to differentiate current certificates from outdated certificates (e.g., Expired CREC, Current CREC).
     - **2.2b. GCP/RCR**: file all Good Clinical Practice and/or Responsible Conduct of Research certificates here, again retaining expired certificates.
     - **2.2c. Professional Licenses**: include here copies of any professional licenses (e.g., RN, LSW, RPh, etc.)
     - **2.2d. Delegation of Responsibility Log**: file here a log that contains all study team member names, study role(s), study tasks, CREC expiration dates, responsibilities start and end dates, signatures, and initials. See the CWRU Delegation of Authority Log template on page 6 of this guide.
   - **2.3 Training Records**
     - **2.3a. Study Training**: file here all documentation of study staff training, including the Study Training Log (example on page 8 of this guide) and any training session tools such as PowerPoint slides, videos, and handouts.
     - ***The following subfolder is not required, but is recommended***
     - **2.3b. MOPs and SOPs**: include any Manual of Procedures or Standard Operating Procedures. As these are updated, do not delete the original versions. All versions should be retained with dates or version numbers in the document name. You may also include an additional subfolder for outdated versions of the MOPs/SOPs to prevent confusion as to which are the most recent/current versions.

3. **IRB-APPROVED PROTOCOL and MODIFICATIONS**
   - **3.1 Study Protocol**: include here all versions of the IRB-approved study protocol, with dates or version numbers in the document name. You may also include an additional subfolder here for outdated versions of the protocol (subfolder 3.1a) to prevent confusion as to which is the most recent/current version.
   - **3.2 IRB Submissions**: file here all IRB Submissions, including the SpartaIRB snapshot of the submission and all IRB correspondence. To further refine and organize, 3 subfolders can be created:

3.2a. Original IRB Submission: use this folder to store the original submission, including the SpartaIRB Snapshot, all submitted supporting documents, and all IRB correspondence related to the submission.

3.2b. Protocol Modifications: use this folder to file all subsequent modifications to the study protocol, including the SpartaIRB Snapshot, all submitted supporting documents, and all IRB correspondence related to the modification submission.

3.2c. Study Team Modifications: use this folder to file all submissions related to internal and/or external study team member changes. Include the SpartaIRB Snapshot, all submitted supporting documents, and all IRB correspondence related to the modification submission.

4. **SPONSOR DOCUMENTS**: include here correspondence with the sponsor, a copy of the grant application, a copy of the approved contract or agreement, Scope of Work (if applicable) and any other documents or reports as applicable to the funding type, i.e. HHS vs Industry. If this is an FDA-sponsored study, Form 1572 should be filed in this folder. Additional subfolders can be created here to further delineate items, e.g. "Correspondence," "Signed Contracts," etc.

5. **STUDY INSTRUMENTS and CONSENT FORMS**
   - **5.1 Consent Forms**: include here all versions of the IRB-approved Consent, Assent, and/or Study Information forms with dates or version numbers in the document name. You may also include an additional subfolder here for outdated versions to prevent confusion as to which is the most recent/current version. Also include in this subfolder any blank copies of the study's Consent Documentation or Consent Checklist forms.
   - **5.2 Blank Set of Study Instruments**: use this folder to store blank copies of data collection instruments, recruitment materials, and checklists. These documents include surveys, scales, questionnaires, call and email scripts, and interview guides. These may be further delineated using additional itemized subfolders, and labeled according to the study's specific design and/or organizational preferences, e.g. "Recruitment," "Timepoint 1," etc. If the forms are updated during the course of the study, do not delete the outdated versions; include dates or versions in the document names. You may also include an additional subfolder here for outdated versions to prevent confusion as to which is the most recent/current version.

6. **ELIGIBILITY and SCREENING**
   - **6.1 Eligibility Criteria**: file a list of the study's inclusion and exclusion criteria. If the criteria changes over the course of the study, include dates or version numbers in the document name. You may also include a subfolder for the outdated versions.
   - **6.2 Screening Log**: file a deidentified screening log that includes information regarding subjects' screening dates, eligibility outcome, reason for ineligibility, consent outcome (completed vs declined), study ID if consented/enrolled and, if available, reason subject declined participation. See sample Screening Log here CCR Forms - CCR Forms - CCR Wiki (cancer.gov)

7. **ENROLLMENT**
   - **7.1 Enrollment Log**
   - **7.2 Identification Key**: if a Subject/Participant ID key is separate from the Enrollment Log, store it in this subfolder.
   - **7.3 Blinding Procedures** (if applicable)
   - **7.4 Randomization Procedures** (if applicable)

8. **REPORTABLE NEW INFORMATION**
   - **8.1 Participant Complaints**: include here all documentation of complaints from study participants, including details such as date, names of study team members involved in complaint or communications, and outcome.
   - **8.2 Adverse Events**: see page 10 of this guide.
   - **8.3 Protocol Deviations**: see page 11 of this guide.
   - **8.4 Unanticipated Problems**: see page 12 of this guide.
   - **8.5 IRB RNI Submissions**: file here documentation related to IRB RNI submissions and outcomes.

9. **STUDY MONITORING**
   - **9.1 DSMB**: if applicable, include here information regarding the Data Safety Monitoring Board or Data Safety Monitor and all DSMB or DSM reports. If not applicable, include a note that no formal DSMB or DSM is utilized or required for this study.
   - **9.2 Internal Data Safety and Quality**: use this subfolder to file documentation of and procedures for internal monitoring/reviews of study data safety and quality, such as responsible parties of the study team, schedule of reviews, checklists, and reports. An additional subfolder can be created here for documentation of CWRU QIP Reviews, including communications, findings, and IRB recommendations/action items.
   - **9.3 Site Monitoring Log**: if applicable, store here the log provided by or created for the outside (not CWRU or UH) site monitors' study visit documentation. This subfolder should also include communications with the site monitors. If not applicable, include a note that no site monitoring is utilized/required for this study.

10. **LABORATORY DOCUMENTS**: file here copies of lab certifications, normal laboratory and reference values and manuals, lab director's CV, and any blank copies of lab orders or procedures for entering orders. If not applicable, include a note that no laboratories or laboratory tests are used for the study.

11. **SPECIMENS**: use this folder to file information regarding biological specimen collection, storage, and tracking such as logs, equipment manuals, and shipping records. If not applicable, include a note that no biological specimens are collected or used for the study.

12. **DRUGS and DEVICES**: if the study does not include drugs or devices, include a note stating such and skip the following subfolders.
    - **12.1 IB, Package Inserts, Device Manuals**: file here the Investigator's Brochure for INDs or IDEs (if available) or the package insert(s)/manuals for approved drugs and devices.
    - **12.2 Label Information**: include here a sample of labels attached to the drugs or devices, if any.
    - **12.3 Drug or Device Accountability**: include here shipping and dispensing records; environmental monitoring/storage logs; records related to defects, repair, or replacement of devices; and any destruction documentation.

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Delegation of Responsibility Log

Use this log to document the roles and responsibilities assigned to each study team member, as well as their signatures and initials. Edit the log after each team member addition/removal or change in responsibilities. Using the Study-Specific Tasks key, assign the appropriate task number(s) in the Study-Specific Tasks column. Note that the key provided is an example and may be changed to more accurately reflect your protocol, if desired.

Investigator and Protocol Information

CWRU IRB Number: STUDY
Principal Investigator(s):
CWRU IRB Expiration Date:
Protocol Title:

Delegation of Responsibility Log

Print Name	Study Role	Study-Specific Tasks	Signature	Initials	CREC Certification Expiration Date	Dates of Responsibilities		PI Approval (PI initials and Date)
						Start Date	End date	

Study Role:

Principal Investigator	Research Coordinator	Research Nurse	Statistician	Other: _____
Co-Investigator	Research Assistant	Research Fellow	Pharmacist	Other: _____

Study-Specific Tasks:

1. Obtain informed consent	6. Data entry	11. Assess AEs/UPs/PDs	16. Data Analysis
2. Study recruitment	7. Sample collection	12. Regulatory/IRB submissions	17. Billing/Finance
3. Confirm eligibility	8. Sample processing, storage, shipping	13. Evaluate study-related test results	18. Other (specify): _____
4. Conduct study visit procedures as per protocol	9. Dispense study drug/device	14. Perform study-related assessments as per protocol	19. Other (specify): _____
5. Data collection/CRF completion	10. Perform drug/device accountability	15. Maintain essential documents, regulatory binder	20. Other (specify): _____

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Training Log

Use this log to document any study-related training conducted for investigators and study team members. Using the Training Topics key, assign the appropriate number(s) in the Topics column. Note that this log and key are an example and may be changed to more accurately reflect your study's training needs.

Investigator and Protocol Information

CWRU IRB Number: STUDY
Principal Investigator(s):
CWRU IRB Expiration Date:
Protocol Title:

Study Training Log				
Training Date	Topic(s) *see key below*	Training Description	Trainee	Trainer
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____
			Name: _____ Signature: _____	Name: _____ Signature: _____

Training Topics:

1. Study Protocol	5. Data Management/Integrity	9. Participant Complaints
2. Study Recruitment	6. Specimen Collection and Handling	10. Other (specify): _____
3. Informed Consent	7. Lab Procedures	11. Other (specify): _____
4. Data Collection	8. AEs, UPs, PDs	12. Other (specify): _____

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Adverse Event Log

Use this log to document any adverse event*, either anticipated or unanticipated, regardless of severity and relationship to study. **See the Investigator Manual, Chapter 27, for guidance on what types of AEs should be submitted to the IRB as Reportable New Information (RNI) within either 3 or 5 business days of discovery.** All others should be reported at the time of Continuing Review or Annual Check-in.

Investigator and Protocol Information

CWRU IRB Number: STUDY
Principal Investigator(s):
CWRU IRB Expiration Date:
Protocol Title:

If the AE is also an Unanticipated Problem, update the Unanticipated Problem Log in addition to this log.

Adverse Event Log														
			Severity of Event**			Please Indicate if the Event Was Expected:		Is This AE also an Unanticipated Problem?		Please Indicate Relationship to Study:			Reported to IRB? If YES, add Date	
Subject ID	Date of Event	Description of Event	Mild	Moderate	Severe	Yes	No	Yes	No	Study-Related	Possibly Study-Related	Not Study-Related	Yes + Date Reported	No

**** Adverse events are any unintended negative experience associated with the study materials or research procedures. Adverse events include both physical and psychological harms.***

***** Severity Rating***
Mild: Easily tolerated symptoms of a minor irritant type causing no loss of time from normal activities. Does not require intervention.
Moderate: A low level of inconvenience or concern; may interfere with daily activities, may require simple therapeutic intervention.
Severe: Incapacitating; interrupts normal daily activities and generally requires systemic therapeutic intervention or hospitalization.

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Protocol Deviation Log

Use this log to document any alteration/modification to the IRB-approved protocol, whether intentional or inadvertent, that is not approved by the IRB prior to its initiation or implementation. If either question is answered "Yes," this indicates a Major Protocol Deviation. **All Major Protocol Deviations should be submitted to the IRB as Reportable New Information (RNI) within 5 business days of discovery.** All Minor Protocol Deviations should be reported at the time of Continuing Review or Annual Check-in.

Investigator and Protocol Information

CWRU IRB Number: STUDY
Principal Investigator(s):
CWRU IRB Expiration Date:
Protocol Title:

Protocol Deviation Log				
Date of Deviation	**Description of Deviation**	**Did the deviation impact subject's rights, safety, or well-being? If yes, report to CWRU IRB within 5 business days and note date RNI submitted.**	**Did the deviation impact the completeness, accuracy, or reliability of the study data? If yes, report to CWRU IRB within 5 business days and note date RNI submitted.**	**Describe the corrective action taken by the investigators to avoid reoccurrence.**

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Unanticipated Problem Log

Use this log to document any Unanticipated Problem*. **See the Investigator Manual, Chapter 27, for guidance on what types of Unanticipated Problems should be submitted to the IRB as Reportable New Information (RNI).**

Unanticipated Problems (UP) may or may not be related to Adverse Events (AE) and/or Protocol Deviations (PD). If an Adverse Event meets ALL 3 of the criteria listed below, then the event is considered an Adverse Event AND an Unanticipated Problem. Document the event on both the UP and AE logs. Similarly, if a Protocol Deviation meets ALL 3 of the criteria listed below, then the event is considered a Protocol Deviation AND an Unanticipated Problem. Document the event on both the UP and PD Logs.

Data breaches may also be UPs. If the data breach results from a deviation to the protocol, that is documented as a Protocol Deviation. However, if a data breach does NOT result from a deviation and meets ALL 3 of the criteria listed below, it would be documented only on this log.

For additional information, see OHRP's guidance here: Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

Unanticipated Problems (UPs) are events that could adversely affect the rights, safety, or welfare of the participants or others (e.g., family members, by-standers, and researcher/team), or which significantly impacts the integrity of research data. An example would be a breach of confidentiality or unintentional destruction of study records. Specifically, a UP is any incident, experience, or outcome that meets all the following criteria:

> ***1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; and***
>
> ***2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and***
>
> ***3. Suggests that the research places subjects or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.***

Unanticipated Problems

Investigator and Protocol Information

CWRU IRB Number: STUDY
Principal Investigator(s):
CWRU IRB Expiration Date:
Protocol Title:

If the Unanticipated Problem (UP) is also an Adverse Event (AE) or related to a Protocol Deviation (PD), update those logs as well.

Unanticipated Problem Log													
			Is the Problem unexpected?		Is the Problem related or possibly related to the research?		Does the Problem suggest a greater risk of harm than previously known?		Is the Problem also an Adverse Event or Protocol Deviation?			Reported to IRB? If YES, add Date	
Subject ID	Date of Event	Description of Event	No	Yes	No	Yes	No	Yes	No	AE	PD	Yes + Date Reported	No